Screening for Lung Cancer

What does the evidence support?

Heidi Roberts, MD, FRCP(C)
Professor of Radiology
Screening – Facts

• Impact of Lung Cancer
• Screening CTs for lung cancer detection
• Lung cancer stage at detection
Impact of Lung Cancer

• **FREQUENT**
  
  Canada 2010:
  
  - 24,200 new diagnoses
  - 20,600 deaths

• **LETHAL**
  
  Lung cancer is the **leading cause of cancer death** for both men and women (30% of all cancer deaths)

  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
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
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Overall
screen-detected lung cancers
I-ELCAP, PMH, Toronto
(~2.3% detection rate)
Screening - Issues to be discussed

- CT technique
- mortality
- nodules and false positives
- radiation exposure – how long screen?
- impact of screening
- who should be screened
- who’s in charge
- present and future
Lung Cancer Screening – Method

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

**PROS**

- detection of tiny nodules (some we don’t care about)
- postprocessing

**CONS**

- ~ 350 images/scan (x2)
  - scrolling
  - storage
- noisy
- reconstruction limited
thicker-slice, low-dose CT e.g., 3 mm

**PROS**
- faster scrolling (workflow)
- storage
- detection of (very) small nodules
- reconstruction

**CONS**
- limitations for
  - postprocessing
  - 3D analyses
  - further research
“Lung Cancer Screening Using LDCT Reduces Deaths”

Nov 4th, 2010
- 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
Single-arm trials: survival

- International Early Lung Cancer Action Program (I-ELCAP)

I-ELCAP
- 27,456
- non-randomized
- 10-year-survival
- up to 92%*

Henschke et al,
New Eng J Med 2006
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

no screen

CT - Dx

screen

Sy - Dx

dead

survival

lead time

survival
overdiagnosis bias

no screen

CT - Dx

screen

death from other cause

no Dx autopsy
randomized trials: mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Year started</th>
<th>Subjects</th>
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<tbody>
<tr>
<td>LSS</td>
<td>USA</td>
<td>CT vs CXR</td>
<td>2000</td>
<td>3318</td>
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<tr>
<td>DANTE</td>
<td>Italy</td>
<td>CT vs obs</td>
<td>2001</td>
<td>2472</td>
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<tr>
<td>NLST</td>
<td>USA</td>
<td>CT vs CXR</td>
<td>2002</td>
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<tr>
<td>NELSON</td>
<td>NL–B</td>
<td>CT vs obs</td>
<td>2003</td>
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<td>DLCST</td>
<td>DK</td>
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<td>2004</td>
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<td>ITALUNG</td>
<td>Italy</td>
<td>CT vs obs</td>
<td>2004</td>
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<td>MILD</td>
<td>Italy</td>
<td>CT vs obs</td>
<td>2005</td>
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<td>LUSI</td>
<td>Germany</td>
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<td>2007</td>
<td>4000</td>
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<td></td>
<td></td>
<td></td>
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<td>&gt;90,000</td>
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National Lung Screening Trial

- 20% mortality benefit
- will change the way how lung cancer screening will be recommended
- impact on health care policies expected

- full publication ~ spring/summer 2011?
- analyses?
- reproducibility?
Lung Cancer Screening

- nodules, nodules, nodules ..... cancer

- false positives

  nodules in the lung that turn out NOT to be cancer
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 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
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<th>Definition</th>
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<tr>
<td>ELCAP *Henschke (\text{Lancet} \ 1999)</td>
<td>any size n=1-6</td>
<td>23.3</td>
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<tr>
<td>Italian SS *Pastorino (\text{Lancet} \ 2003)</td>
<td>6mm</td>
<td>29</td>
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<td>LSS (NCI) *Gohagan (\text{Chest} \ 2004)</td>
<td>4mm</td>
<td>20.5</td>
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<td>Mayo *Swenson (\text{Radiology} \ 2005)</td>
<td>any</td>
<td>51</td>
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<td>Toronto (n=1000) *Roberts (\text{Can Ass Rad J} \ 2007)</td>
<td>5mm</td>
<td>25.7</td>
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<tr>
<td>Toronto (n=3352) *Menezes, Roberts (\text{Lung Cancer} \ 2009)</td>
<td>5mm</td>
<td>18</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

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<th>Low-Risk Patient†</th>
<th>High-Risk Patient‡</th>
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Lung Cancer Screening – nodules

- follow up of nodules
- Fleischner criteria

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* Diameter
† Lead to screening
§ No further follow-up
‖ Repeat scan if unchanged
Lung Cancer Screening – nodules

- follow up of nodules
- Fleischner criteria

| High-Risk Patient: | Follow-up CT at 12 mo; if unchanged, no further follow-up
|--------------------|---------------------------------------------------|
| Follow-up CT at 6–12 mo then at 18–24 mo if no change | Initial follow-up CT at 3–6 mo then at 9–12 and 24 mo if no change
| Same as for low-risk patient |
Lung Cancer Screening – nodules

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

• solid lesions $< \sim 5$ mm
  – “negative”, no follow up

annual repeat
nodule follow up

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

- solid lesions $5 - 10$ (15?) mm
  - surveillance of growth
  - doubling time $30 - 360 = \text{malignant}$
doubling time 72 days
combined small cell-large cell neuroendocrine carcinoma

3 months
3 months

mucinous adenocarcinoma
nodule follow up

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

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

adenocarcinoma

3 months
nodule follow up

• solid lesions < ~ 5 mm
  – no follow up
• solid lesions 5 – 10 mm
  – surveillance of growth
• part-solid lesions
  – risk of malignancy relates to size and growth of solid component
• non-solid lesions < 8 mm
  – “negative”, no follow-up
– non-solid (ground glass)
  • ~34% malignant
  • risk ↑ when round and > 1.5 cm
  • bronchioloalveolar carcinoma (BAC) or invasive adenocarcinoma with BAC features
overdiagnosis bias?

3 months

no growth

biopsy: malignant cells

surgical resection

1.1 cm bronchioloalveolar carcinoma, no invasion
overdiagnosis bias?
growth rate ~380 days
nodule follow up

- solid lesions
  - surveillance of growth
- Computer Assisted Diagnosis?
CAD volumetry

- ? precision
  - reproducibility or repeatability
  - the degree to which further measurements or calculations show the same or similar results

![Diagram showing low precision and high accuracy compared to high precision and low accuracy]
CAD volumetry

• interscan variability
• nodule volume influenced by
  – patient position, heart pulsation, inspiration levels
  – segmentation
CAD volume comparison

- 20 patients with lung metastases
- two additional low-dose CTs (30mAs, 120 kVp)
- reconstructed 1.0 mm thickness / 0.7 mm increments
- patients got off and on the table between scans
Nodule CAD – volumetry

- precision
- dependent on nodule shape and segmentation
  - extremely high for spherical nodules
  - threshold for calling increased volume: 15%
  - decreased for nonspherical nodules
  - threshold for calling increased volume: 30%
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
examples: screen-detected nodules
example: lung nodules

CT for hemoptysis  

bx planning CT
List Serv

• Lung Cancer Online Discussion hosted by the Surgical Oncology Program (SOP) at Cancer Care Ontario
  – case presentation
  – online discussion
List Serv – Case #1

- A 72 year old female, non-smoker, diabetic presents with a **suspicious nodule** found on screening CT scan....
- CT chest shows a **1.2 cm nodule with indistinct borders**, non-calcified, and in the posterior segment of the right upper lobe of the lung. All mediastinal nodes are < 1 cm.
List Serv – Case #1

• ~ 20 responses
• from surgeons, oncologist, (not respirologists)
• all (but two) ACTION

• “…avoid errors of omission, never mind errors of commission”
The USPSTF concludes that the evidence is insufficient to recommend for or against screening asymptomatic persons for lung cancer with either low-dose computed tomography (LDCT), chest radiographs, sputum cytology, or a combination of these tests.

I recommendation.
U.S. Preventive Services Task Force

- The USPSTF found fair evidence that screening with LDCT, chest radiographs, or sputum cytology can detect lung cancer at an earlier stage than lung cancer would be detected in an unscreened population;

- however, the USPSTF found poor evidence that any screening strategy for lung cancer decreases mortality.

- because of the invasive nature of diagnostic testing and the possibility of a high number of false-positive tests in certain populations, there is potential for significant harms from screening.
U.S. Preventive Services Task Force

- The USPSTF found fair evidence that screening with LDCT, chest radiographs, or sputum cytology can detect lung cancer at an earlier stage than would be detected in an unscreened population;
- however, the USPSTF found poor evidence that any screening strategy for lung cancer decreases mortality.
- because of the invasive nature of diagnostic testing and the possibility of a high number of false-positive tests in certain populations, there is potential for significant harms from screening.

The USPSTF could not determine the balance between the benefits and harms of screening for lung cancer.
false positives

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

[Wagnet, Roberts, et al. 2010]
**PET**

- for solid lesions > 7mm
- no uptake in BAC/adenocarcinoma

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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
Lung Cancer Screening

Radiation risk

annual scanning
- low-dose
- how long?
- how often?

baseline 50 – 55 years
annual / biennial until ~ 75 years

proposal
• first annual
• if no change - biennial
lung cancer screening - incidental findings

- 19% of all participants
  - 22% cardiovascular
  - 78% noncardiovascular (mostly liver and kidney)
  - most commonly recommended imaging follow up: abdominal ultrasound

- 10 malignancies
  - 2 multiple myeloma
  - 1 lymphoma
  - 6 breast cancers
  - 1 thyroid cancer

[Kucharczyk M, Roberts et al. CARJ 2011]
Canadian Tobacco Use Monitoring Survey 2009

• “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.”
### 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
  4,050 Stage 1 (75%)
- *ever* smokers 13,200 lung cancers
  9,900 Stage 1
Lung Cancer Screening – selection

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)
Lung Cancer Risk Assessment Model

individual profile

classification regression model that utilizes
socio-demographic factors, smoking exposure, medical
and radiographic data

- age
- smoking history
- history of COPD (self-reported)
- chest X-ray in last 3 years
- family history
- education
- body mass index

M Tammemagi & PLCO Study Group
Performance of Risk Assessment Model

Tammemagi PLCO model

• applied to participants of the Pan-Canadian Early Lung Cancer Detection Study

• detection rate >2.6%

  + spirometry
  + biomarker
  + sputum analysis
Lung Cancer Screening – network

family practice / respirology, etc.
  risk assessment
  smoking counselling

medical imaging
  low-dose
  nodule detection
  nodule follow up
  biopsies

incidental findings

thoracic surgery
  immediate surgery
  minimal invasive
  (VATS) resection

“Screening is a process, not a procedure”
Lung Cancer Screening - April 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 - April 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
Lung Cancer Screening - the Future

what does the evidence support?

- ready for the paradigm shift
- methods
  - low-dose CT
  - detection and definition of “positives” (lung nodules)
  - definition of false positives
  - stringent protocol for follow up
- selection
  - “at risk” population
  - case finding rather than screening
- collaborating network
  - screening program