Lung Cancer Screening Using Low-Dose CT

Where are we?

Heidi Roberts, MD      Narinder Paul, MD
Disclosures

• None
Lung Cancer

• *It touches all of us!!*

• Canada 2012:
  25,600 new diagnoses
  20,100 deaths

• USA 2012:
  226,160 new diagnoses
  160,340 deaths
Lung Cancer

- Leading cause of cancer death for both men and women
- 30% of all cancer deaths
- Annual mortality exceeds that of breast, prostate, colon, kidney, liver, and melanoma combined
- >50% of new cases diagnosed at advanced stage
Lung Cancer

Stage IV

15% 5YS survival
Lung Cancer

Stage I

80% 5YS survival
Screening for lung cancer

• simple, safe, precise and validated test

• ’70’s, ’80’s CXR screening

• No impact on mortality

Oken et al, JAMA Oct 2011
Screening for lung cancer

Low Dose CT
- 120 kV
- 40-60 mA
- 1 mm – 1.25 mm
- widely available
Low-dose CT
Lung Cancer Screening - Detection

- Nodule detection - not an issue
- Prevalence of lung cancer ~ 1.5% - 2.5%
- Tumour stage ~ 80% stage 1

screen-detected lung cancers
I-ELCAP, PMH, Toronto
peripheral, small, solid, semi-solid, GGO
(~2.3% detection rate)
Single-arm trials: Survival

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

I-ELCAP
- 27,456 (4782 PMH)
- non-randomized
- 10YS
- up to 92%*

Survival vs. Mortality

- longer survival $\neq$ reduced mortality

- survival biased by
  - lead time bias
  - overdiagnosis
  - length time bias
lead time bias

no screen

CT - Dx

Sy - Dx

dead

survival

lead time
overdiagnosis bias

no screen

screen

CT - Dx

death from other cause

no Dx autopsy
Length time bias = screening test tends to capture slower growing tumours which are more likely to have a favourable prognosis.
# randomized trials: mortality end point

<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>
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<td>2472</td>
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<td>NLST</td>
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<td>CT vs CXR</td>
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> 90,000
“Lung Cancer Screening Using LDCT Reduces Deaths”

Nov 4th, 2010

NLST initial trial results, showed 20% mortality reduction among trial participants screened with low-dose CT compared to CXR screened subjects.
NLST – lung cancer survival

Probability of survival: Participants with lung cancer

Years from randomization

CT arm lung cancer
CXR arm lung cancer

courtesy of NLST
National Lung Screening Trial

• **The facts:** 20% mortality benefit

• **The hope:** change recommendations for lung cancer screening

impact on health care policy
Where are we?
Screening - Issues to be discussed

• nodules and false positives
• radiation exposure – how long screen?
• cost-effectiveness
• who should be screened
• who’s in charge
• present and future
Screening - Issues to be discussed

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Lung Cancer Screening – nodules

• 5.1% - 51.4% of patients have nodules

• 80-99% are benign

• how deal with all of the nodules?

Bepler et al, Cancer Control, 2003
Screening CT results

- no nodules
- small nodules
- large nodules
Screening CT results

• no nodules
• small nodules
• large nodules

“negative” annual repeat
Screening CT results

- no nodules
  - “negative” annual repeat

- small nodules
  - “positive” 1-3 months follow up, biopsy, etc.

- large nodules
  - “positive” 1-3 months follow up, biopsy, etc.
## positive screening CT

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition</th>
<th>%</th>
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<tr>
<td>ELCAP <em>Henschke</em> <em>Lancet</em> 1999</td>
<td>1-6mm</td>
<td>23.3</td>
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<td>Italian SS <em>Pastorino</em> <em>Lancet</em> 2003</td>
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<td>20.5</td>
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<td>Mayo <em>Swenson</em> <em>Radiology</em> 2005</td>
<td>any</td>
<td>51</td>
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<td>Toronto (n=1000) <em>Roberts</em> <em>Can Ass Rad J</em> 2007</td>
<td>5mm</td>
<td>25.7</td>
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<td>Toronto (n=3352) <em>Menezes, Roberts</em> <em>Lung Cancer</em> 2009</td>
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<td>18</td>
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<tr>
<td>NLST 2011</td>
<td>4mm</td>
<td>27.3</td>
</tr>
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</table>
(false) positive screening CT

- smaller threshold size for a qualifying nodule = larger number of “positive screening CT” scans

Toronto (n=3352) Menezes, Roberts Lung Cancer 2009 5 mm 18
NLST 2011 4 mm 27.3

proposal from the I-ELCAP 7 / 8 mm

Lung Cancer Screening

• how to deal with all of the nodules?
  – Define threshold of nodule size
  – Surveillance
    • protocol
    • size + growth
nodule follow up (5mm)

• solid lesions ≤5 mm → annual repeat
  - “negative”, no follow up
nodule follow up (5mm)

• solid lesions ≤ 5 mm
  – no follow-up

• solid lesions 5 – 10 mm
  – surveillance of growth (rpt LDCT at 3 mth)
  – doubling time 30 – 360 days = malignant
doubling time 72 days

combined small cell-large cell neuroendocrine carcinoma
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
3 months

same size, higher density

adenocarcinoma
nodule follow up

- solid lesions \( \leq 5 \text{ mm} \)
  - no follow-up

- solid lesions 5 – 10 mm
  - surveillance of growth

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

3 months follow up
examples: screen-detected nodules

baseline

3 months follow up
false positives

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

Wagnetz, Roberts, et al; AJR
Screening - Issues to be discussed

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Lung Cancer Screening

Radiation Risk - Low Dose Chest CT - NLST

- 96 CT scanners at NLST sites, 2003-2007
- mean CTDI$_{vol}$ = 3.4 mGy (S.D.=1.7 mGy)
- mean Effective Dose = 2.0 mSv (S.D.=1.0 mSv)
- Range = 0.5 – 7.0 mSv

- F. Larke et al at RSNA 2008 (SSG18-09)
Lung Cancer Screening

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- standard chest CT: 8 - 9 mSv
- screening chest radiograph: 0.08 – 0.12 mSv
- transatlantic flight: 0.25 mSv
- mammography: 0.7 mSv

F. Larke et al at RSNA 2008 (SSG18-09)
Screening – how long?

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

![Graph showing 10 year mortality for lung cancer by smoking status](image)

courtesy N Young, NZ
Screening – how long?

- risk to die from lung cancer $\uparrow$ 55 years – 75/80 years

![Graph showing 10 year mortality for lung cancer by smoking status](image)
Lung Cancer Screening

Timeline for screening: 50 – 55 yrs to 75 - 80 yrs
How often? annual / every 2-3yrs?
Lung Cancer Screening

Proposal

• baseline + 1 annual
• if no change - biennial
Screening - Issues to be discussed

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Lung Cancer Screening – Feb 2013

- 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 – Feb 2013

- 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 – Feb 2013

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disguised screening
“emphysema, COPD, hemoptysis”
full dose, enhanced CT
non-standardized follow up of nodules
Lung Cancer Screening – Whom?

NOT everybody

limit advertisements and promotion

“Demand a CAT Scan” advertising campaign
who should be screened

people at risk
SMOKING AND CARCINOMA OF THE LUNG
PRELIMINARY REPORT

BY

RICHARD DOLL, M.D., M.R.C.P.
Member of the Statistical Research Unit of the Medical Research Council

AND

A. BRADFORD HILL, Ph.D., D.Sc.
Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council

"public health classic"
Risk Factor #1: Smoking

- 10 pack-year?
- 30 pack-year?
- second hand smoking?
Risk Factor \textit{Age}

- risk to die from lung cancer \quad 55 \text{ years – 75 \text{ years}}

\begin{center}
\begin{tikzpicture}
\begin{axis}[
    title={10 year mortality for lung cancer by smoking status},
    xlabel={Age (years)},
    ylabel={deaths/100 men},
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    ytick={0,5,10,15,20,25,30,35},
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    legend style={at={(0.5,0.1)}, anchor=north},
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\addplot coordinates {
(25,0) (30,0) (35,0) (40,0) (45,0) (50,0) (55,0) (60,0) (65,0) (70,0) (75,0) (80,0) (85,0)
};
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};
\end{axis}
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\end{center}

courtesy N Young, NZ
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 – Whom?

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

Inadequate as sole criteria for risk
Lung Cancer Risk Assessment Model
Pan-Canadian Lung Cancer Study

individual profile

predictive regression model

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
Lung Cancer Risk Assessment Model
Pan-Canadian Lung Cancer Study

- detection rate >2.6%
  - + spirometry
  - + biomarker
  - + sputum analysis

M Tammemagi & PLCO Study Group
Screening - Issues to be discussed

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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"
Screening - Issues to be discussed

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Lung Cancer Screening – April 2013

• cannot be prevented- it is happening now!

• need for quality control
• need for updated guidelines
Lung Cancer Screening recent guidelines

- International Association for the Study of Lung Cancers (IASLC) – July 4, 2011
- National Comprehensive Cancer Network (NCCN) – November 4, 2011
- American Lung Association (ALA) – April 23, 2012
- American Cancer Society (ACS) – January 11, 2013

...
Lung Cancer Screening recent guidelines

- most guidelines follow NLST
- recommends low-dose CT screening for
  1. current or former smokers
  2. age 55 to 74
  3. smoking history of at least 30 pack-years
- general population should not be screened
- chest x-rays are not recommended
- screening not an alternative to smoking cessation
- screening useful when access to treatment centers
Summary

Lung Cancer Screening

• 1. Defined the screening population
• 2. Outlined the technical requirements of CT Screening
• 3. Algorithm for follow up of positive screening cases
• 4. Explained why it is not the SOC in Canada
• 5. Canadian outlook - hopeful