Screening for Lung Cancer

What does the evidence support?

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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**

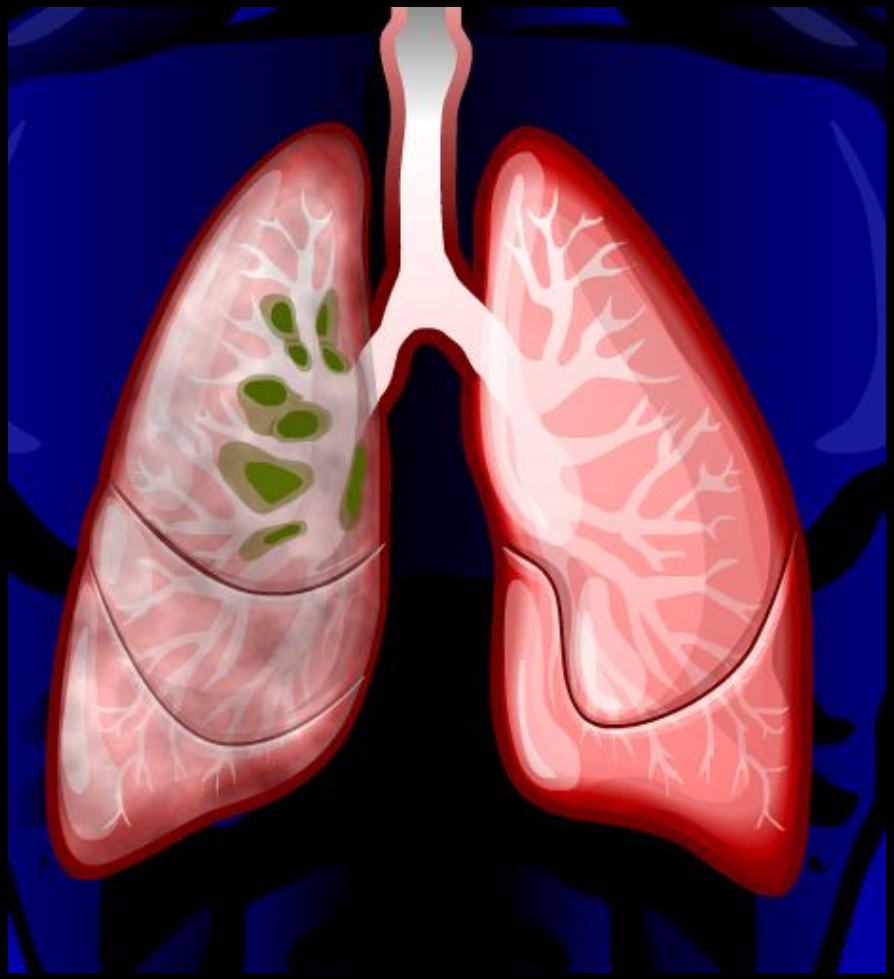
  lung cancer is the leading cause of cancer death for both men and women (30% of all cancer deaths)

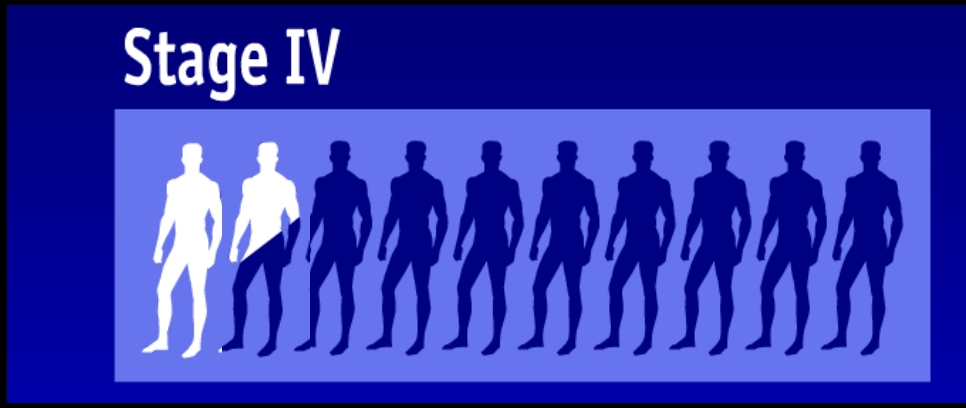
  lung cancer kills more people annually than breast, prostate, colon, kidney and liver cancer, and melanoma combined

- more than 50 percent of new lung cancer cases will be diagnosed at a very late stage

overall 5-year survival ~ 15%

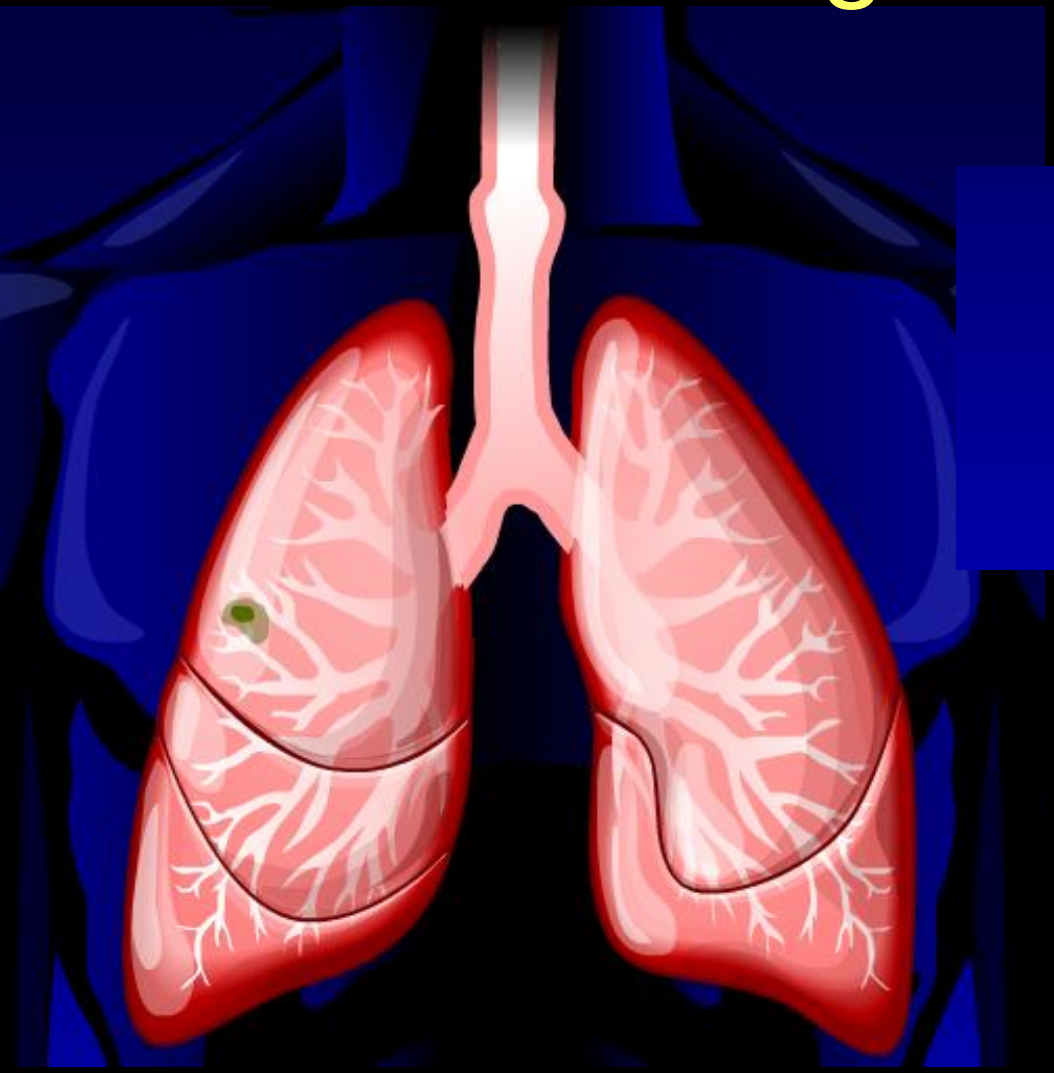
Lung Cancer



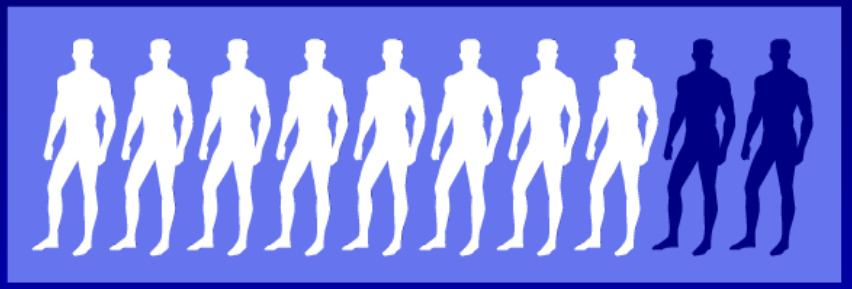


15% survival

Lung Cancer



Stage I



80% survival

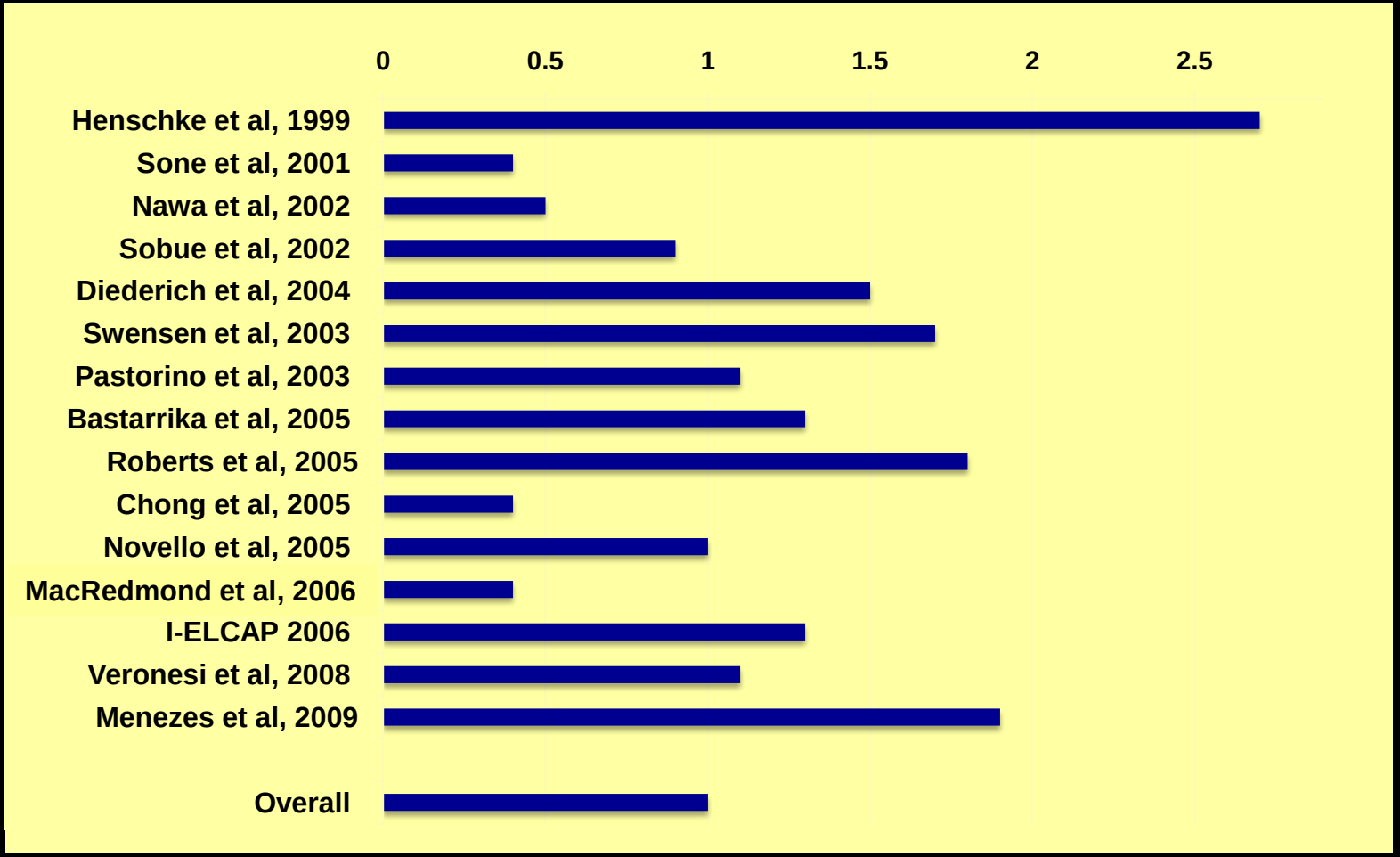
Lung Cancer Screening - Detection

high prevalence and incidence

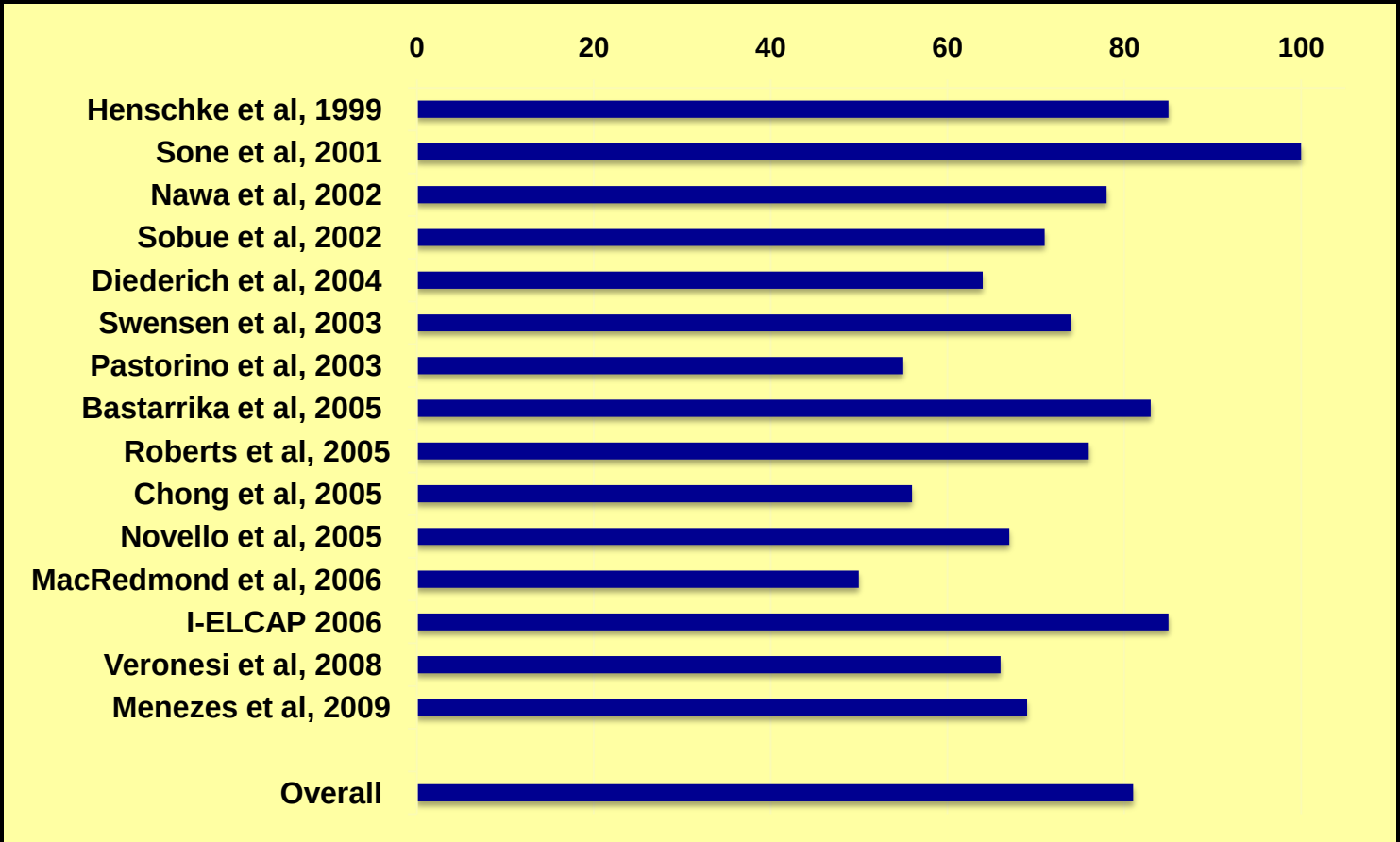
of early stage lung cancer detected at LDCT

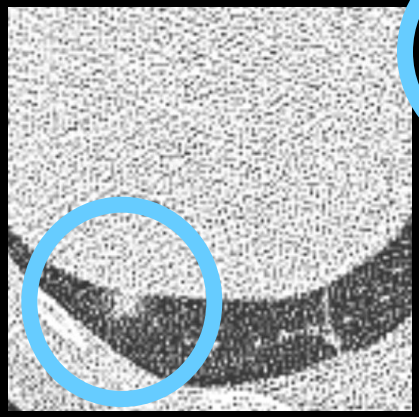
[Bellomi et al. Cancer Imaging 2009, Pastorino Brit J Cancer 2010]

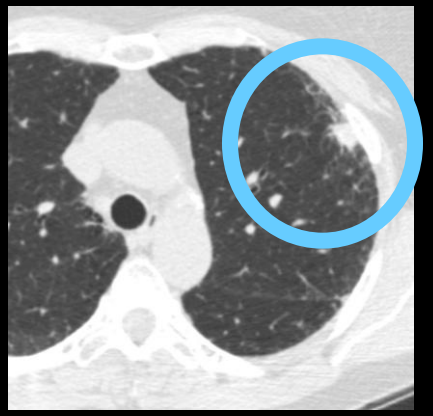
Lung cancer prevalence [%]



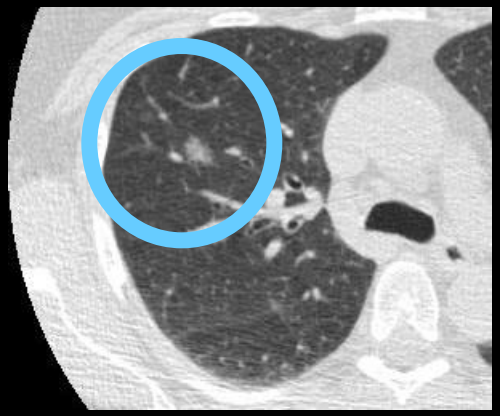
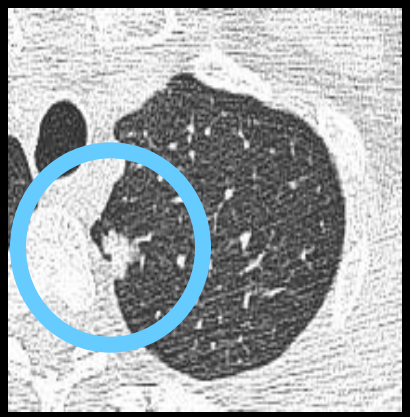
early stage lung cancers [%]





screen-detected lung cancers
I-ELCAP, PMH, Toronto
(~2.3% detection rate)

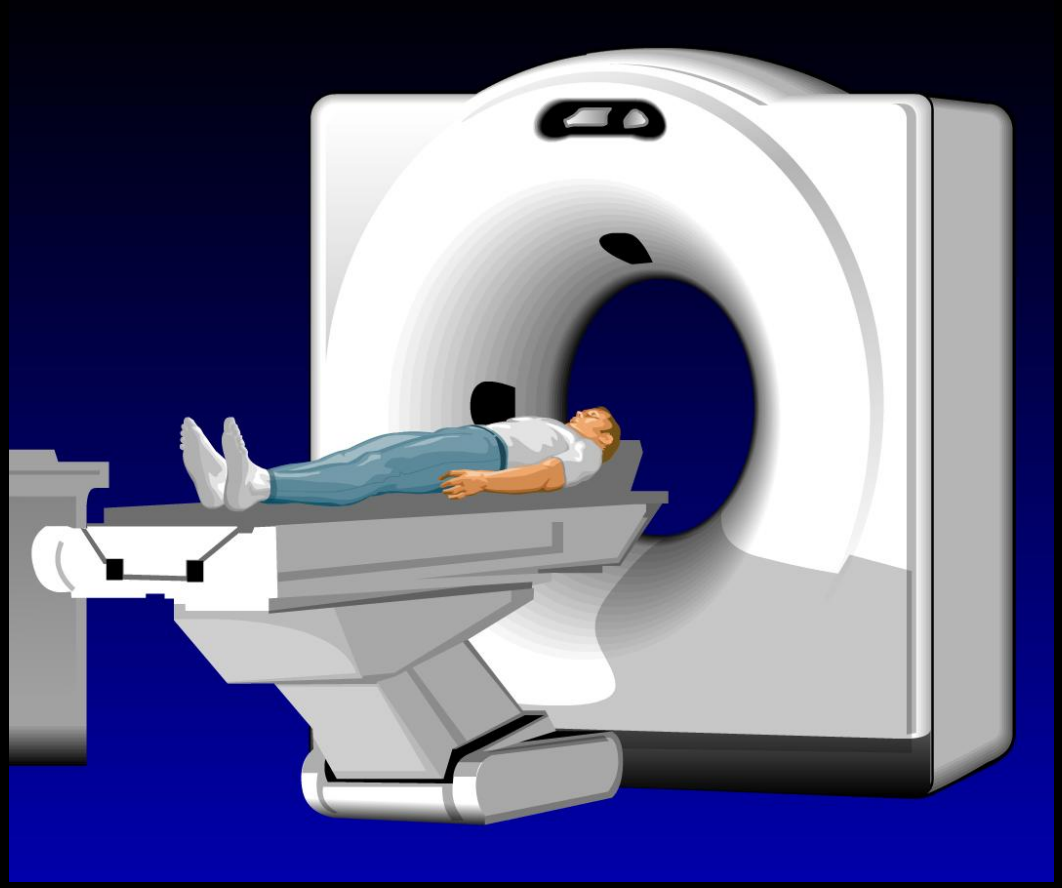



Screening - Issues to be discussed

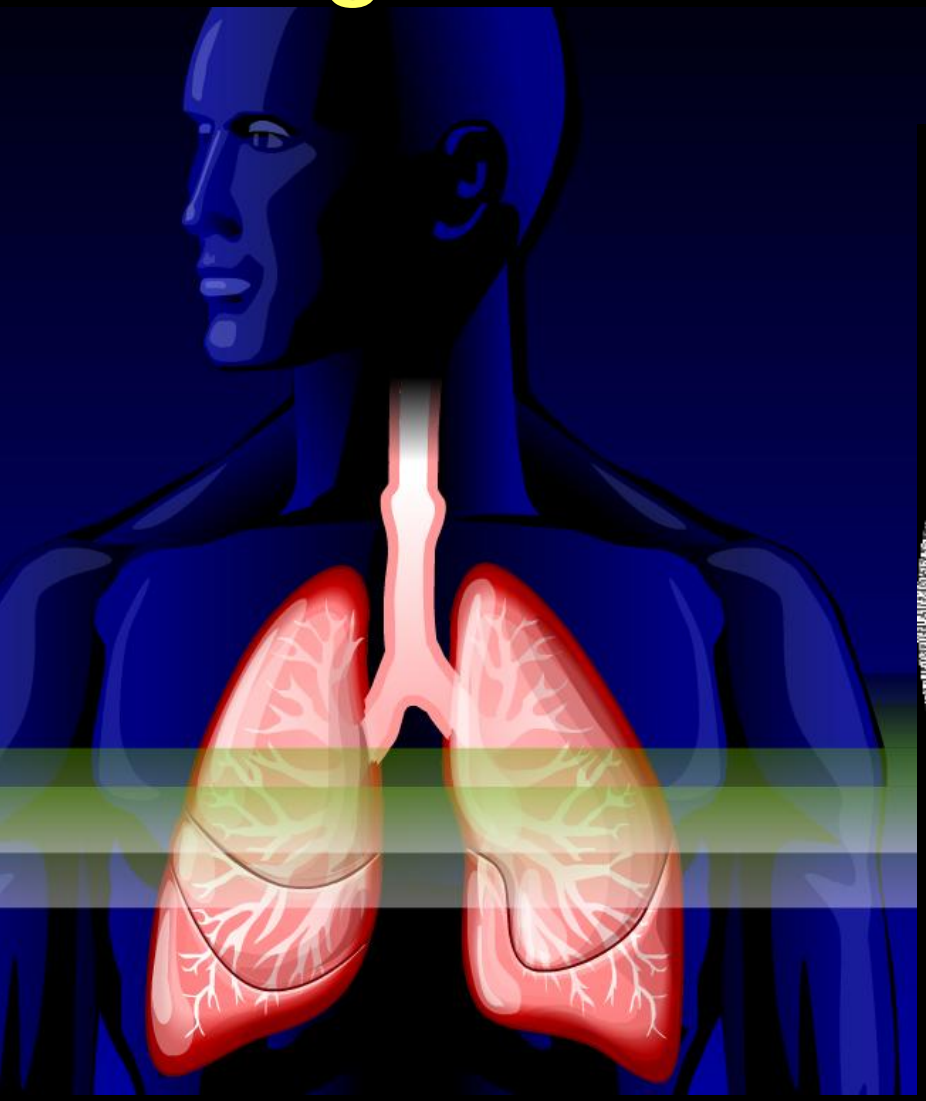
- CT technique
- mortality
- nodules and false positives
- radiation exposure – how long screen?
- impact of screening
- who should be screened
- who’s in charge
- present and future

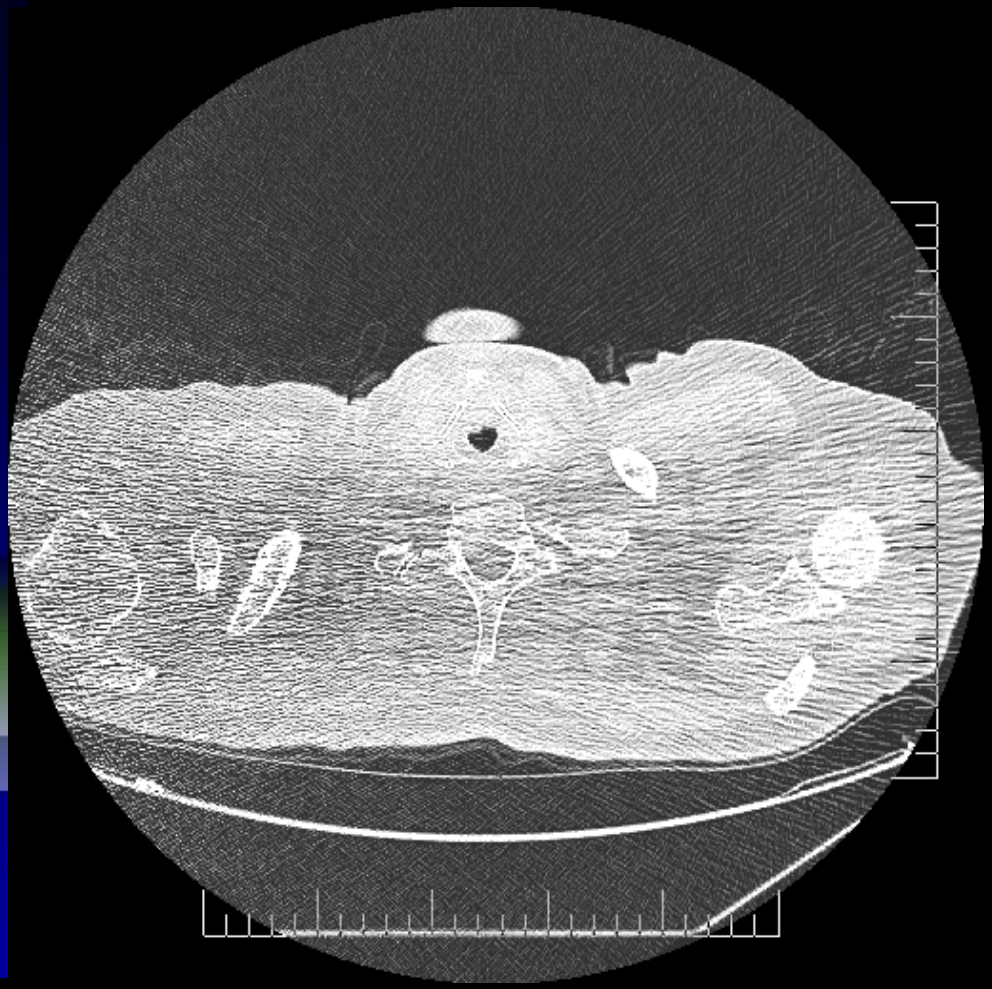
Lung Cancer Screening – Method

- low-dose
- 40-60 mA
- 120 kV
- 1 mm – 1.25 mm

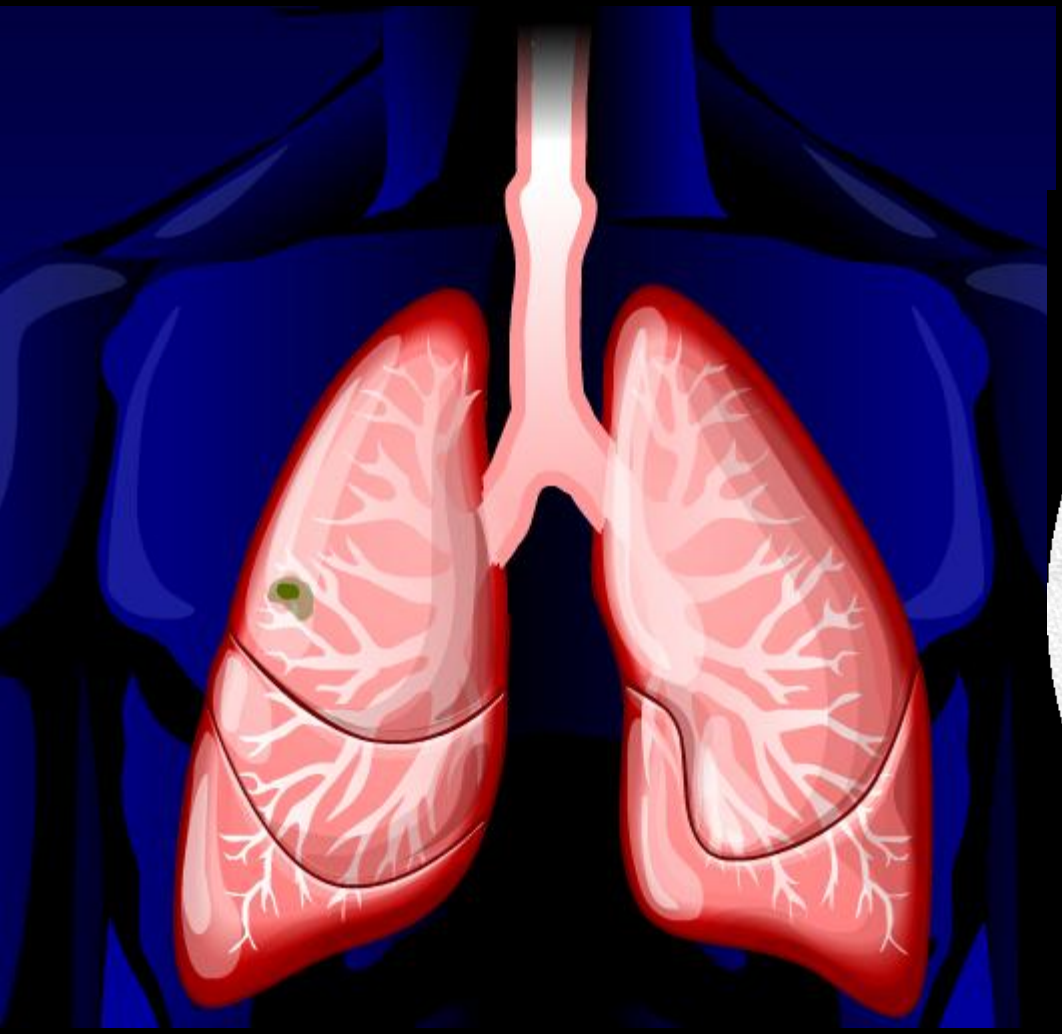


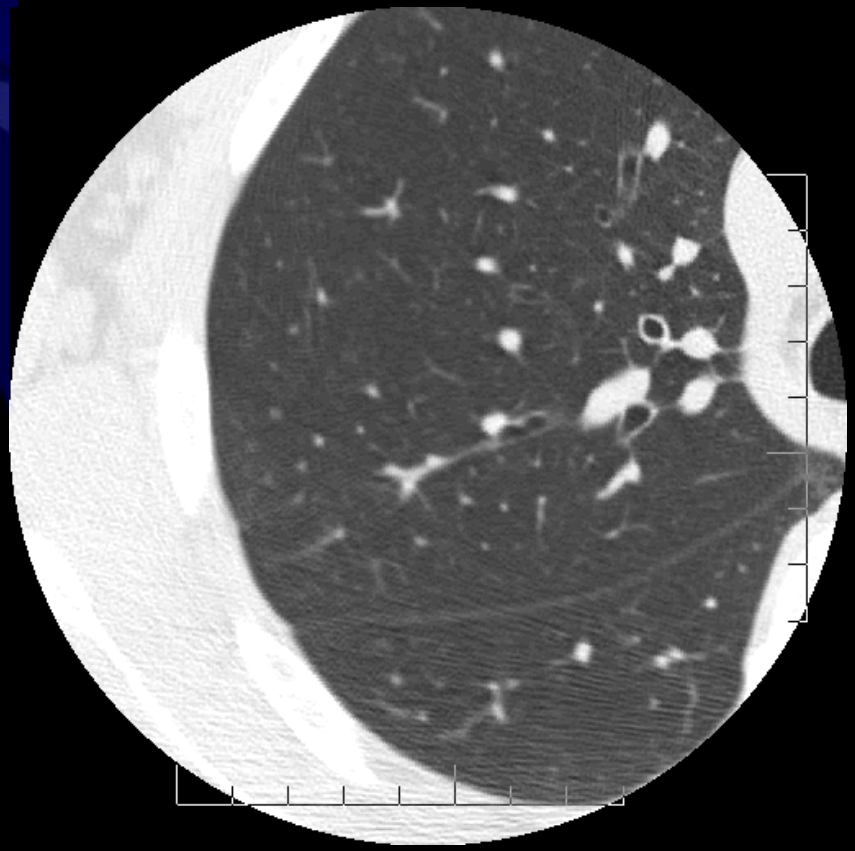
Lung Cancer Screening – Method





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

thestar.com

CBC

“Lung Cancer Screening Using LDCT Reduces Deaths”

Nov 4th, 2010

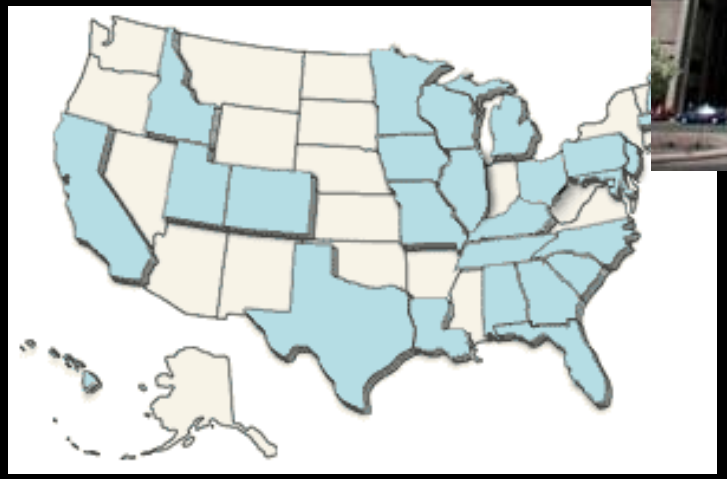
- on November 4, 2010

- 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

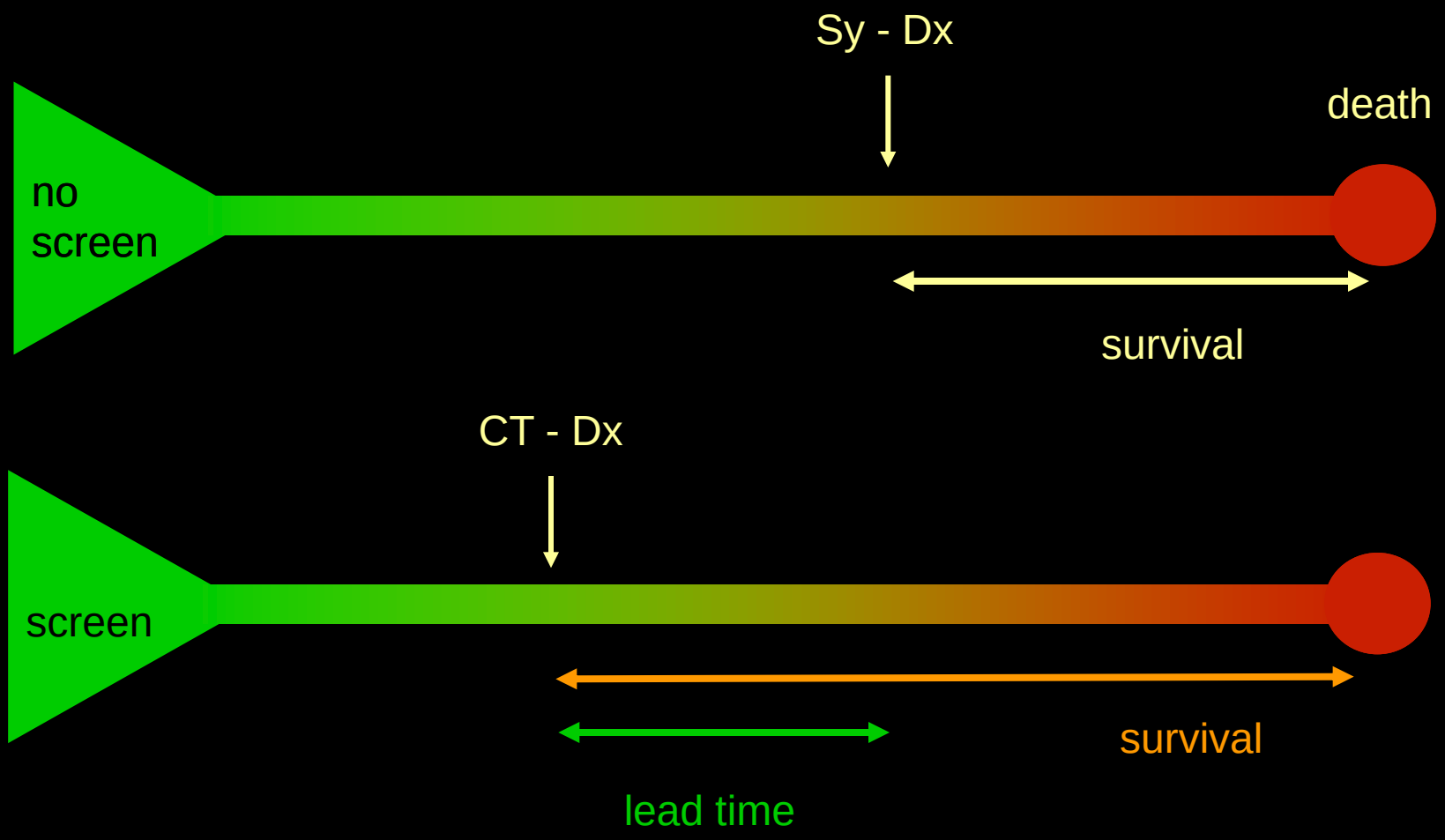
survival vs. mortality

- 10-year survival up to 92%

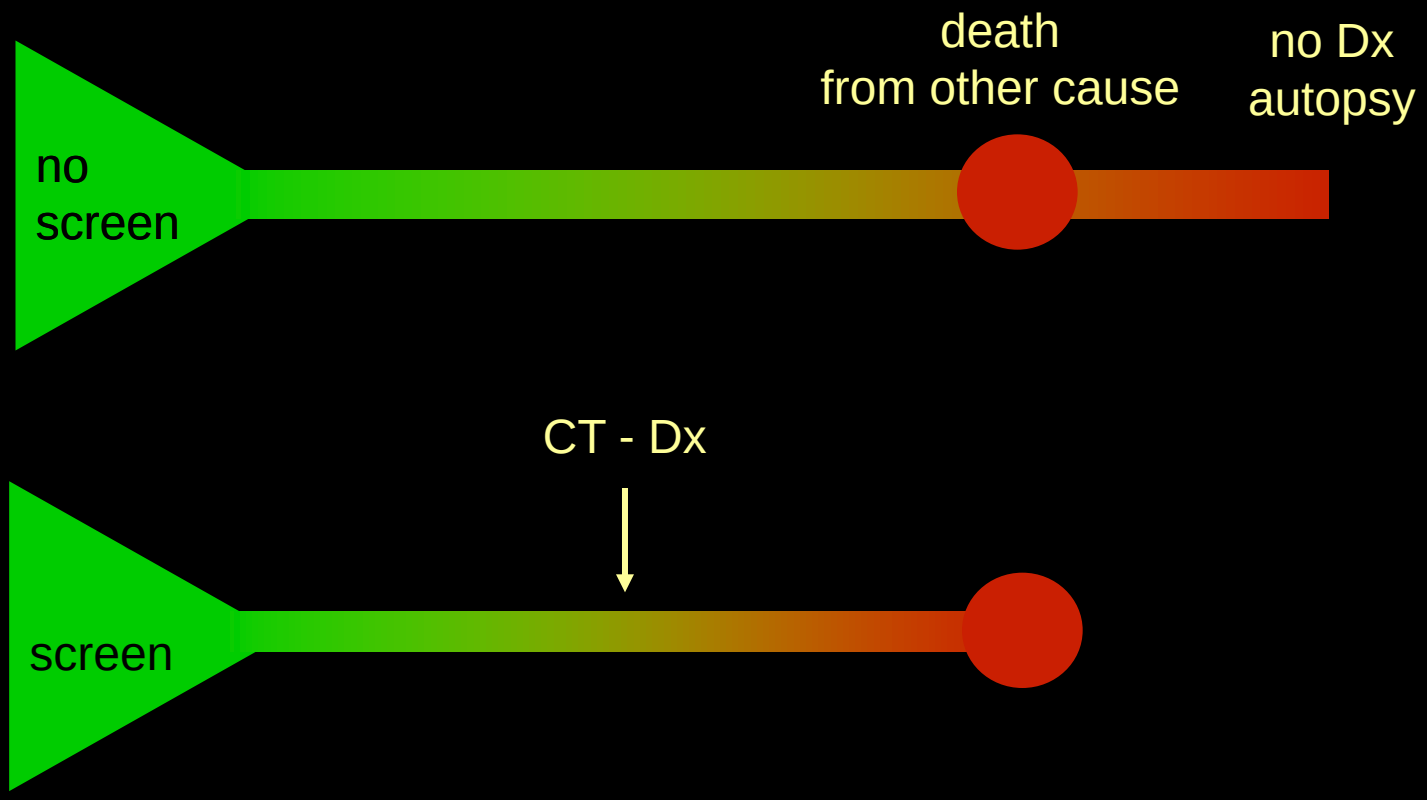
[I-ELCAP New Eng J Med 2006]

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

lead time bias



overdiagnosis bias



randomized trials: mortality

Study	Country	Design	Year started	Subjects
LSS	USA	CT vs CXR	2000	3318
DANTE	Italy	CT vs obs	2001	2472
NLST	USA	CT vs CXR	2002	53000
NELSON	NL–B	CT vs obs	2003	15822
DLCST	DK	CT vs obs	2004	4104
ITALUNG	Italy	CT vs obs	2004	3206
MILD	Italy	CT vs obs	2005	4479
LUSI	Germany	CT vs obs	2007	4000
				> 90,000

National Lung Screening Trial

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

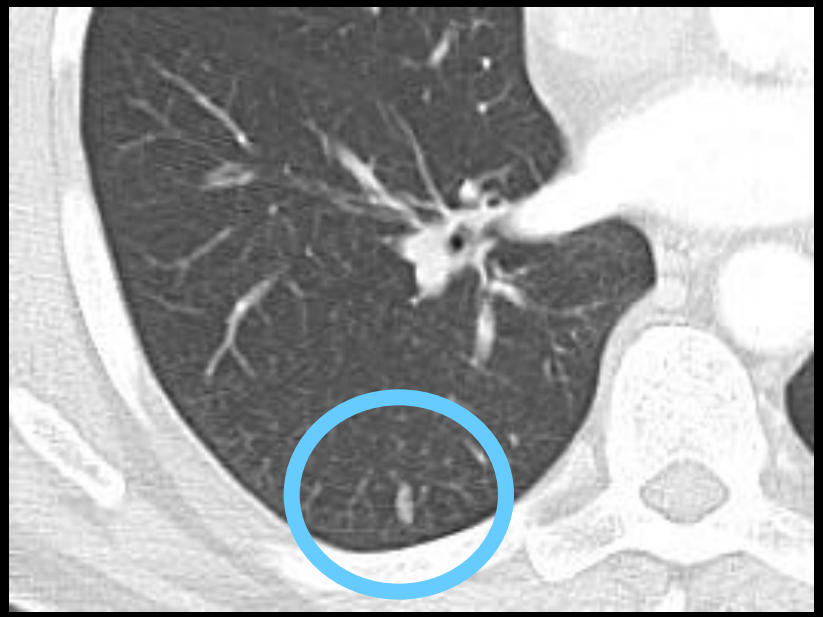
- "negative" without nodules → annual repeat
- "negative" with (small) nodules → annual repeat
- "positive" large nodules → 1 – 3 month follow up CT
  other interventions

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

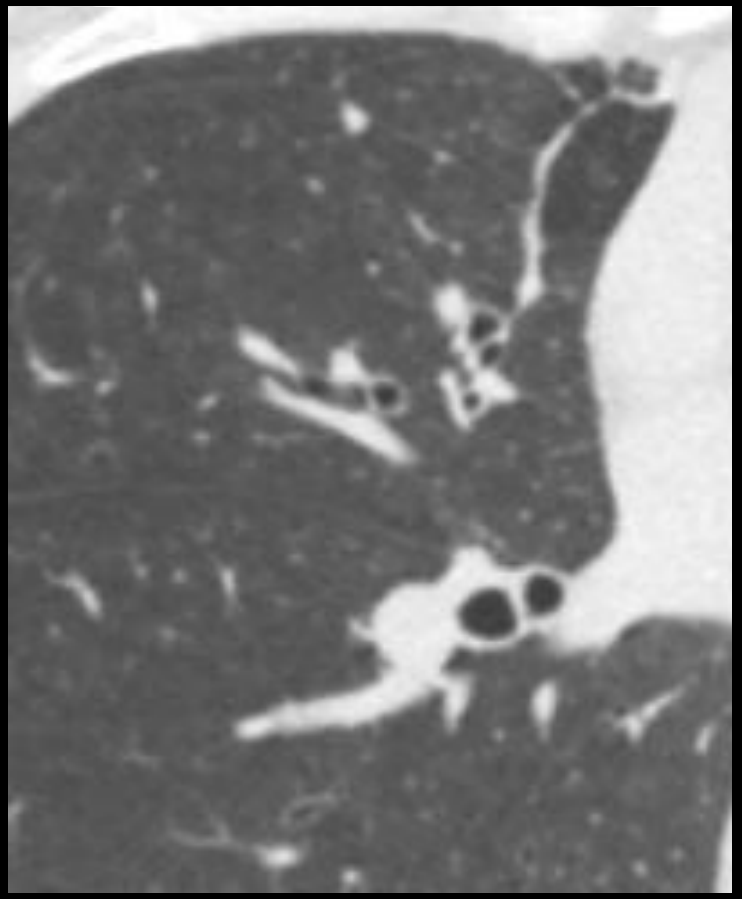
Lung Cancer Screening – nodules

– what is NOT a nodule?



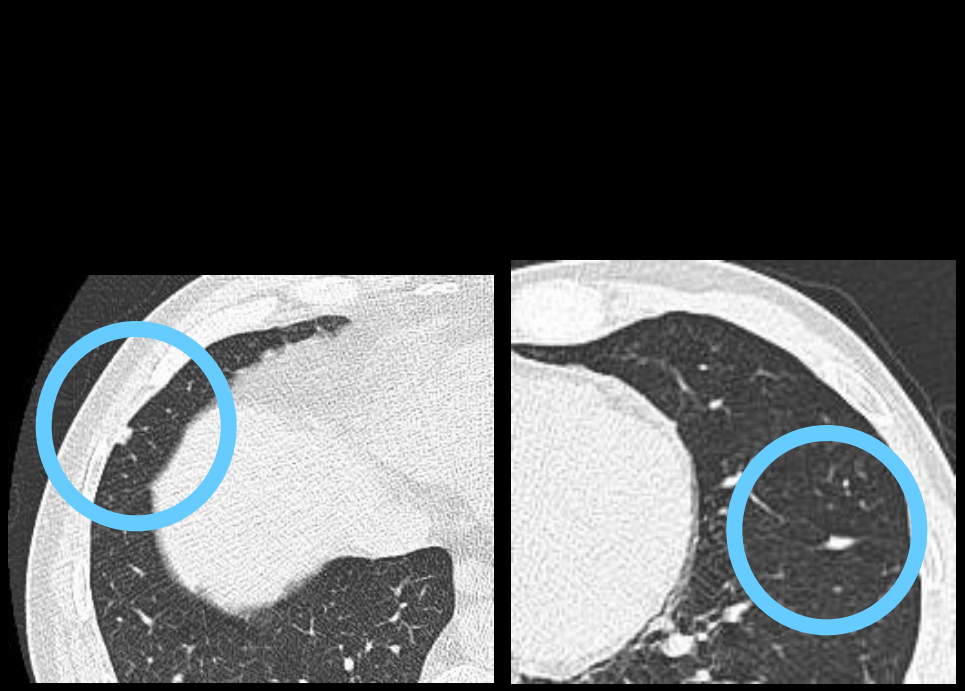
Lung Cancer Screening – nodules

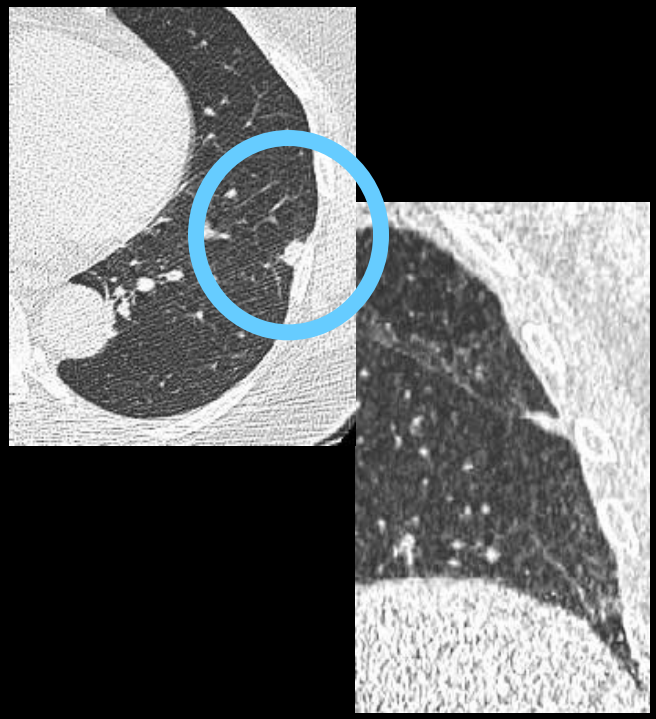
– what is NOT a nodule?



Lung Cancer Screening – nodules

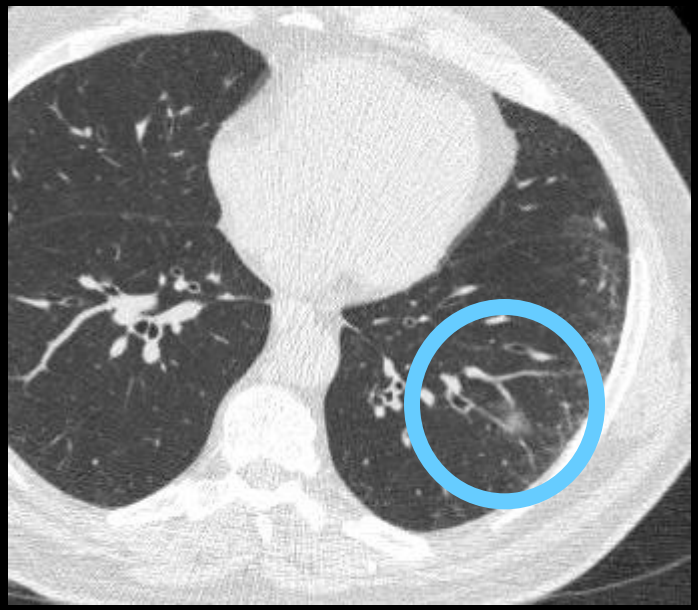
– what is NOT a nodule?





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

positive screening CT

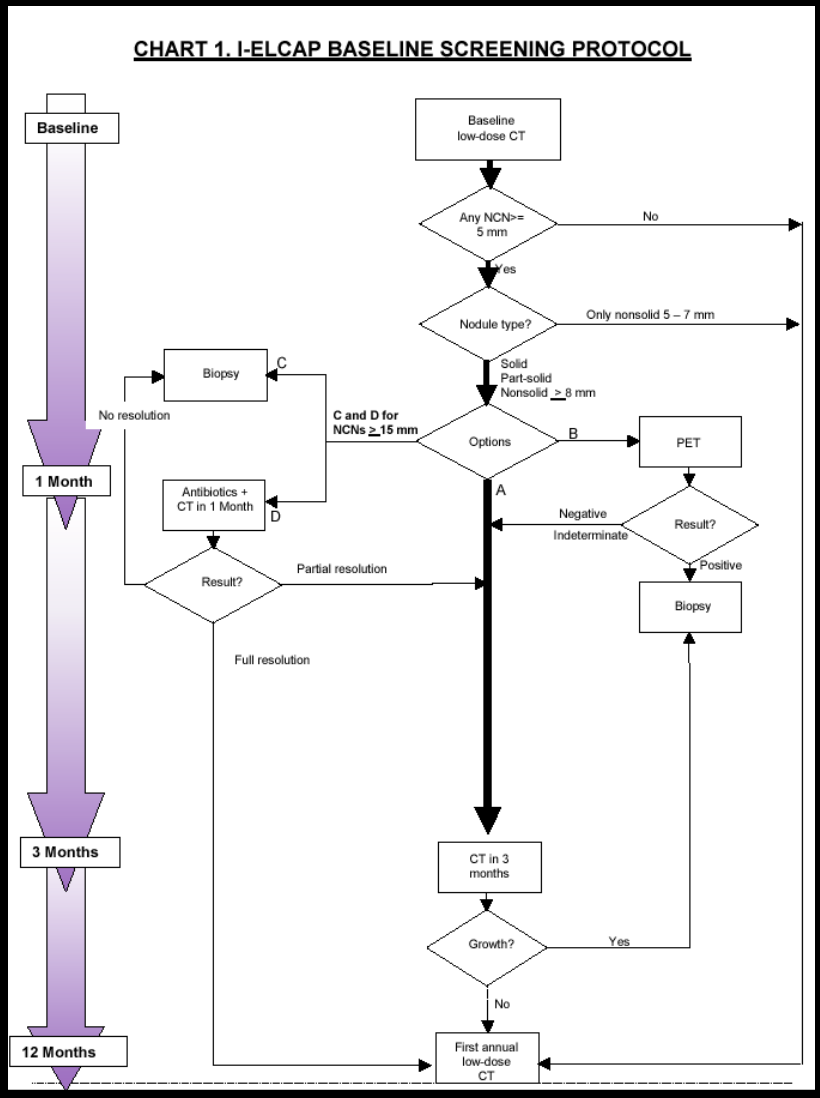
	definition	%
ELCAP *Henschke Lancet 1999*	any size n=1-6	23.3
Italian SS *Pastorino Lancet 2003*	6mm	29
LSS (NCI) *Gohagan Chest 2004*	4mm	20.5
Mayo *Swenson Radiology 2005*	any	51
Toronto (n=1000) *Roberts Can Ass Rad J 2007*	5mm	25.7
Toronto (n=3352) *Menezes, Roberts Lung Cancer 2009*	5mm	18

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

Nodule Size (mm)*	Low-Risk Patient†	High-Risk Patient‡
≤4	No follow-up needed§	Follow-up CT at 12 mo; if unchanged, no further follow-up‖
>4–6	Follow-up CT at 12 mo; if unchanged, no further follow-up‖	Initial follow-up CT at 6–12 mo then at 18–24 mo if no change‖
>6–8	Initial 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
>8	Follow-up CT at around 3, 9, and 24 mo, dynamic contrast-enhanced CT, PET, and/or biopsy	Same as for low-risk patient

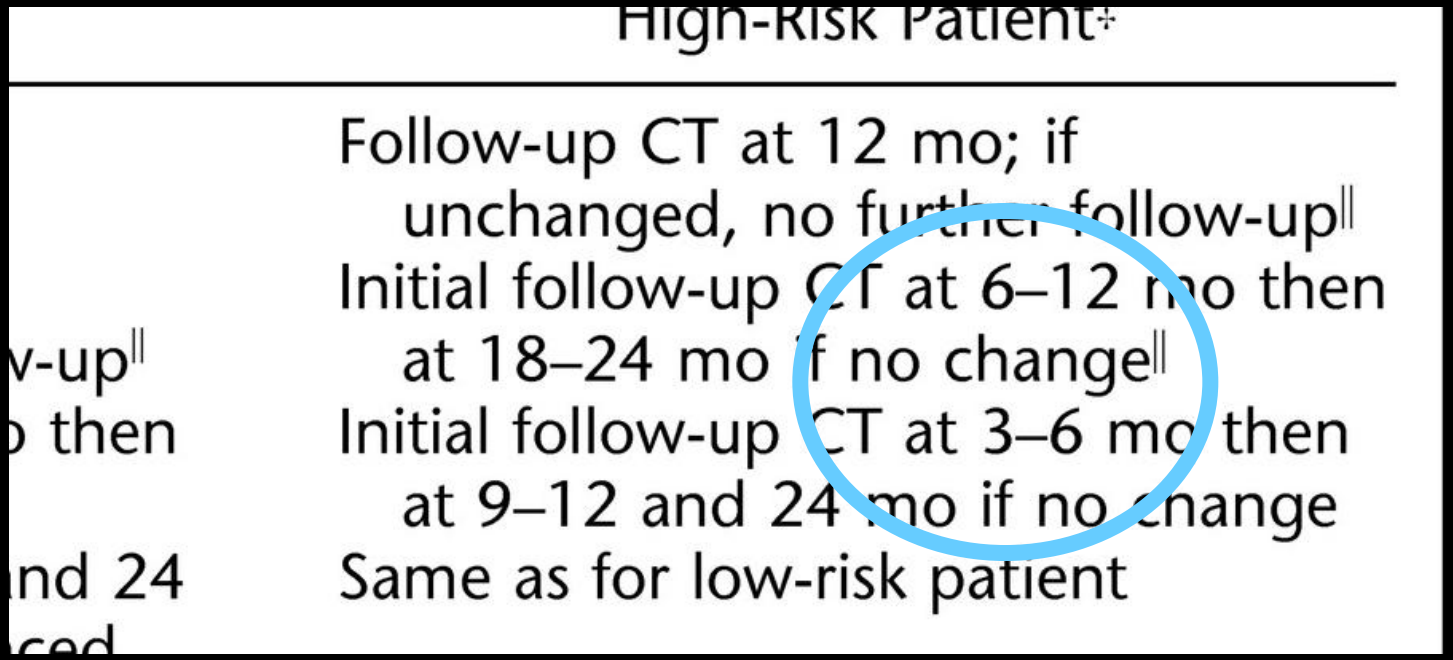
Lung Cancer Screening – nodules

- follow up of nodules
- Fleischner criteria

Nodule Size (mm)*	Low-Risk Patient†
≤4	No follow-up needed§
>4–6	Follow-up CT at 12 mo; if unchanged, no further follow-up‖
>6–8	Initial follow-up CT at 6–12 mo then

Lung Cancer Screening – nodules

- follow up of nodules
- Fleischner criteria



	High-Risk Patient*
v-up‖	Follow-up CT at 12 mo; if unchanged, no further follow-up‖
o then	Initial follow-up CT at 6–12 mo then at 18–24 mo if no change‖
nd 24	Initial follow-up CT at 3–6 mo then at 9–12 and 24 mo if no change
ced	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

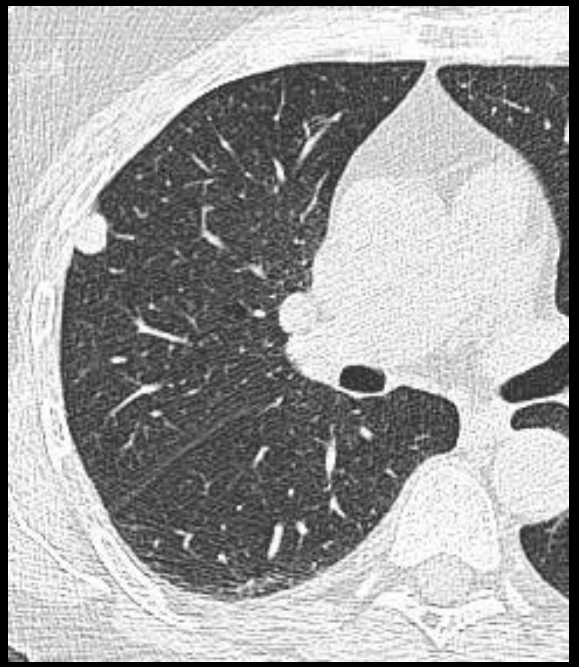
→ annual repeat

nodule follow up

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

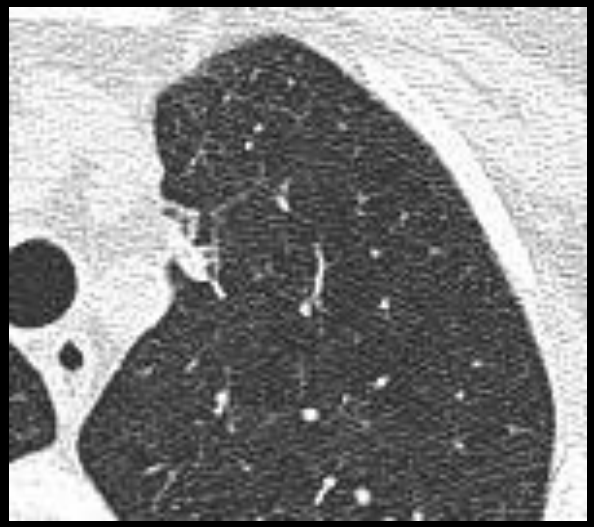
- solid lesions 5 – 10 (15?) mm
  - surveillance of growth
  - doubling time 30 – 360 = malignant

3 months

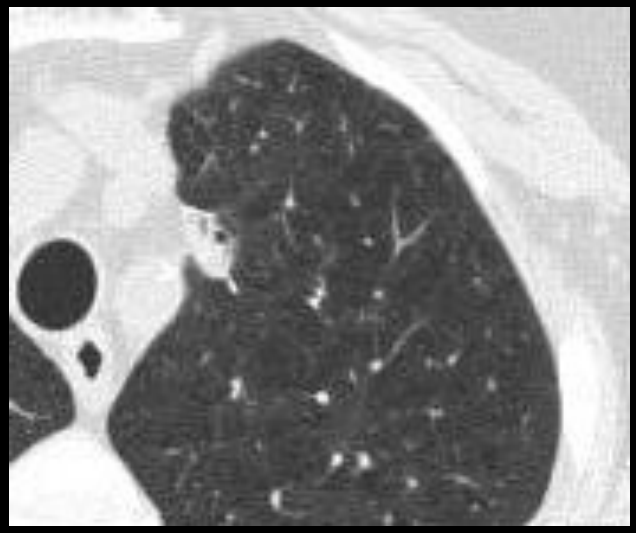


doubling time 72 days

combined small cell-large cell neuroendocrine carcinoma



3 months



mucinous adenocarcinoma

nodule follow up

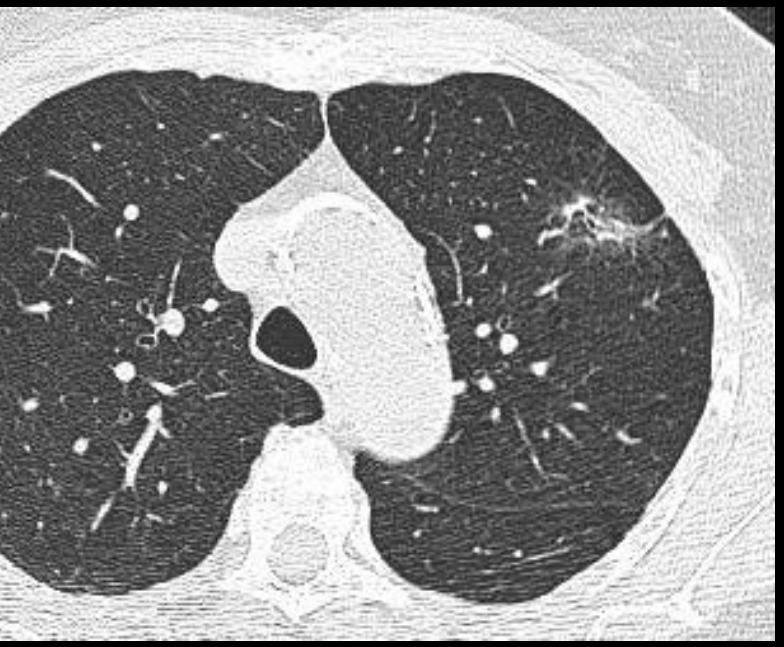
- solid lesions $< \sim 5$ mm
  - no follow up
- solid lesions 5 – 10 mm
  - surveillance of growth

- part-solid lesions
  - risk of malignancy relates to size and growth of solid component

3 months

same size, higher density

adenocarcinoma



3 months

measurement?

adenocarcinoma

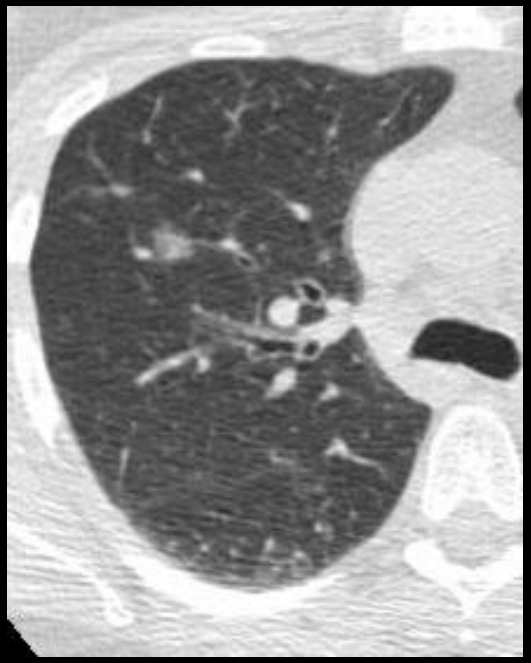
nodule follow up

- solid lesions $< \sim 5$ 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

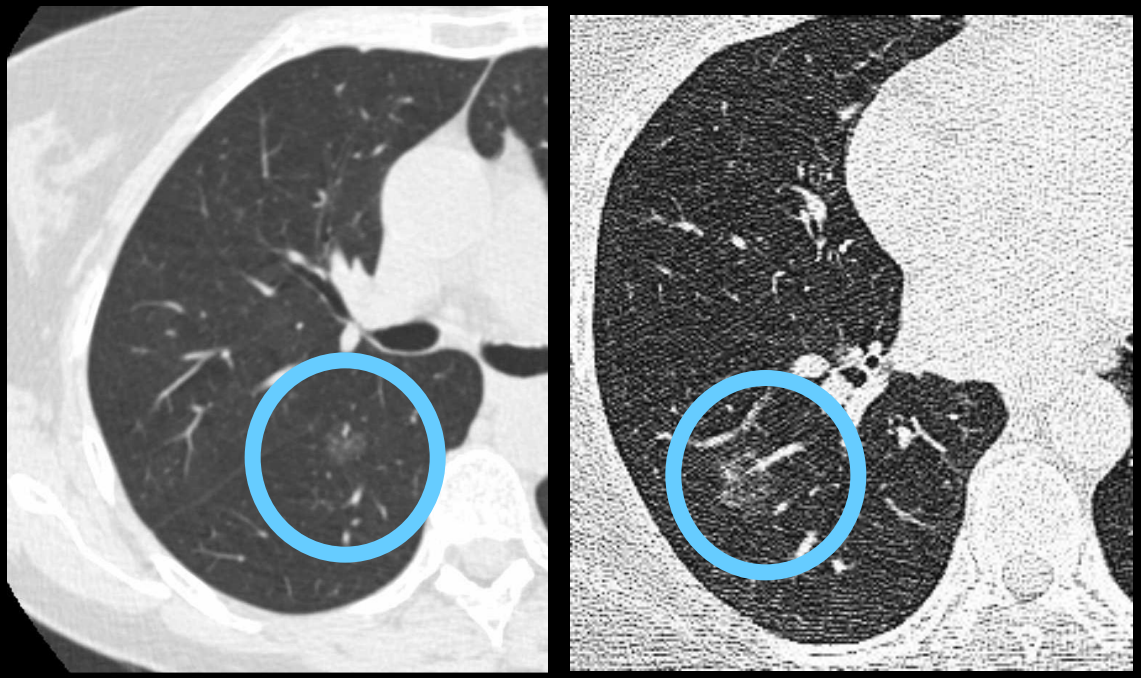


no growth

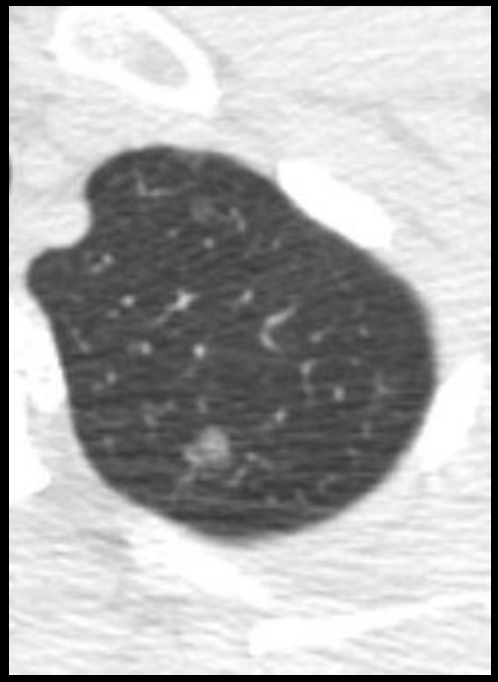
biopsy: malignant cells

surgical resection

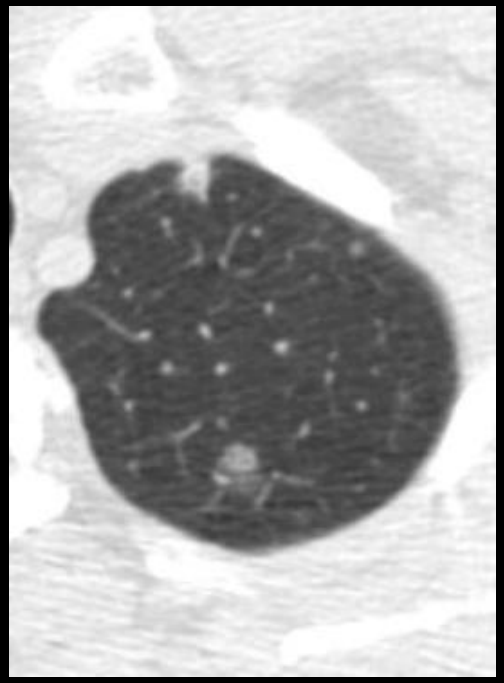
1.1 cm bronchioloalveolar carcinoma, no invasion



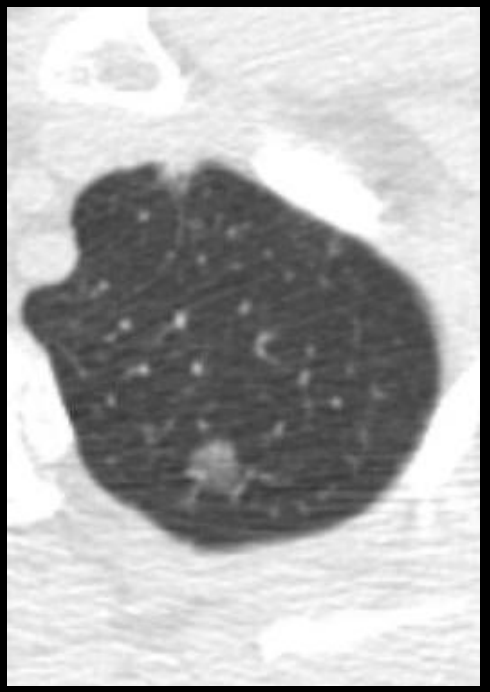
overdiagnosis bias ?



July 2007



March 2008



July 2008

growth rate ~380 days

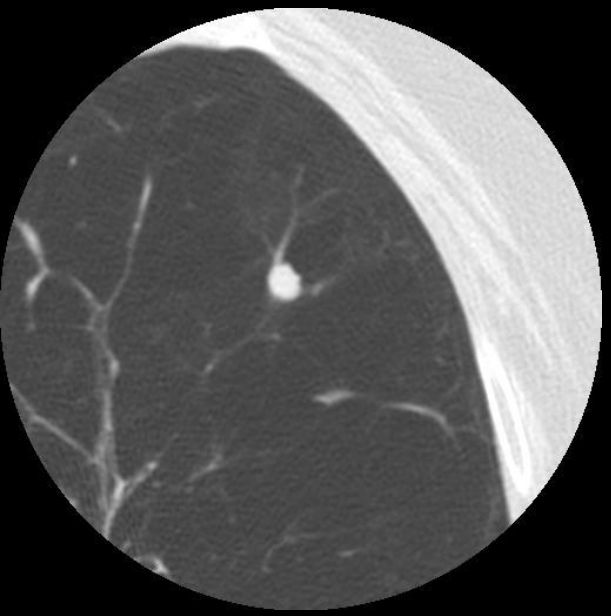
2006

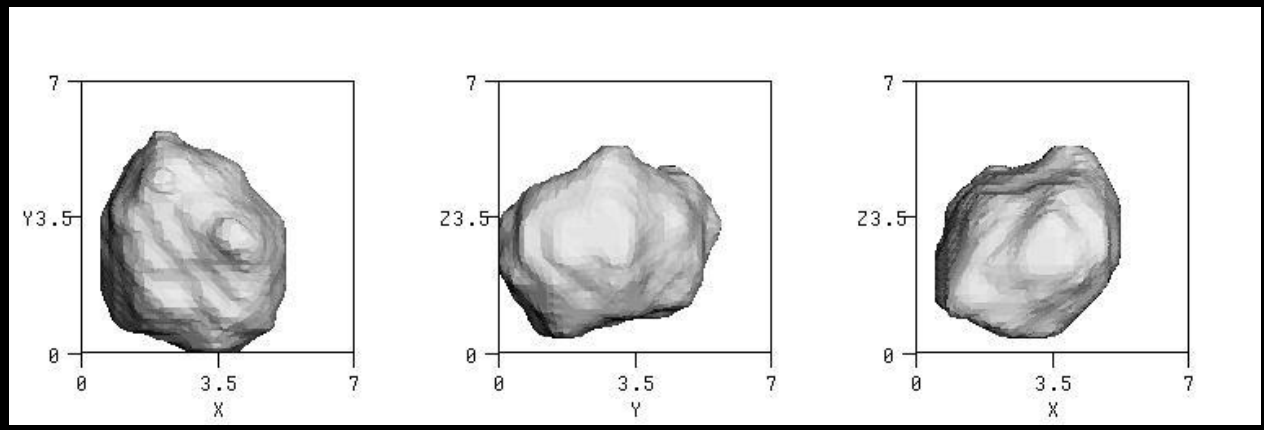
2007

2010

nodule follow up

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

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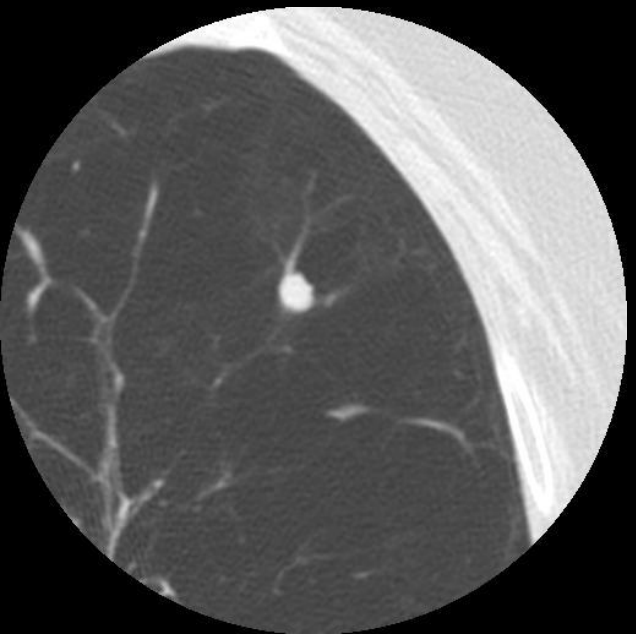

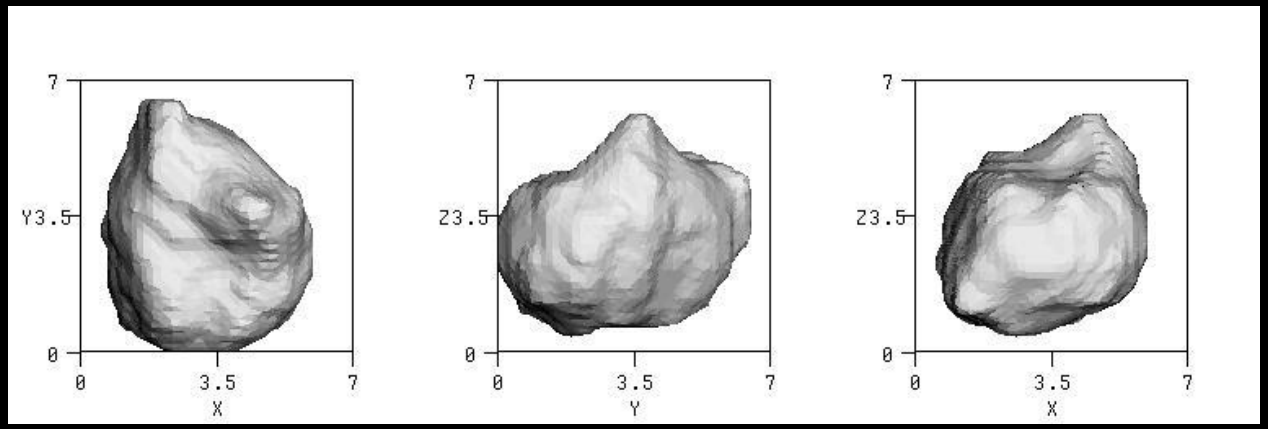
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CAD volumetry

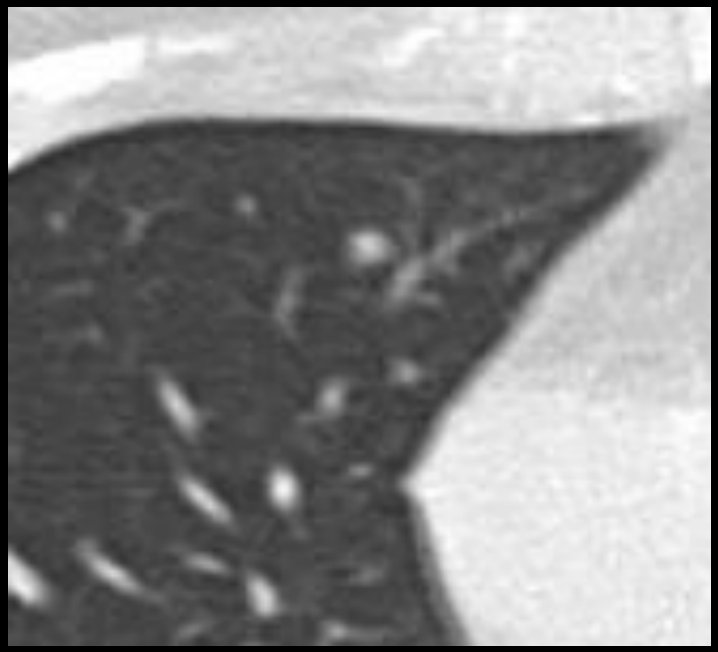
- ? precision
  - reproducibility or repeatability
  - the degree to which further measurements or calculations show the same or similar results

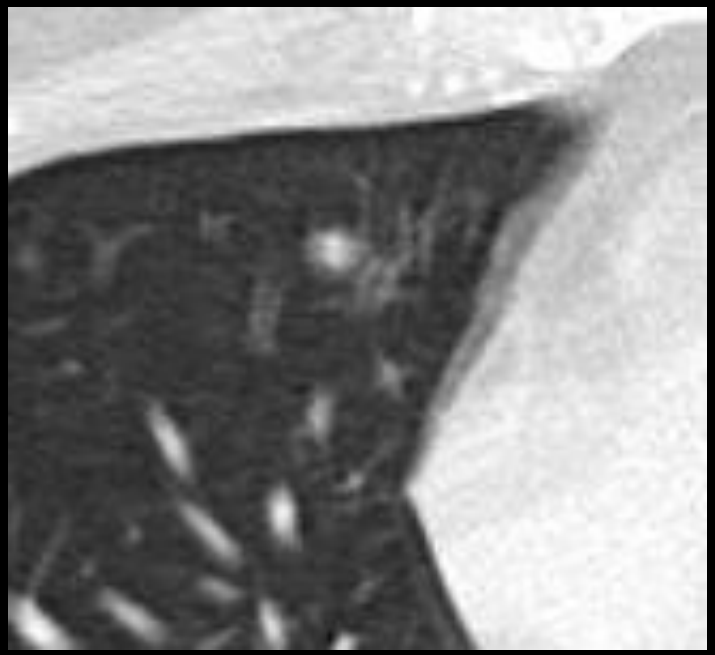
low precision
high accuracy

high precision
low accuracy

CAD volumetry

- interscan variability
- nodule volume influenced by
  - patient position, heart pulsation, inspiration levels
  - segmentation





CAD volume comparison

- Gietema et al, *Radiology* 2007; 245: 888-894
- 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

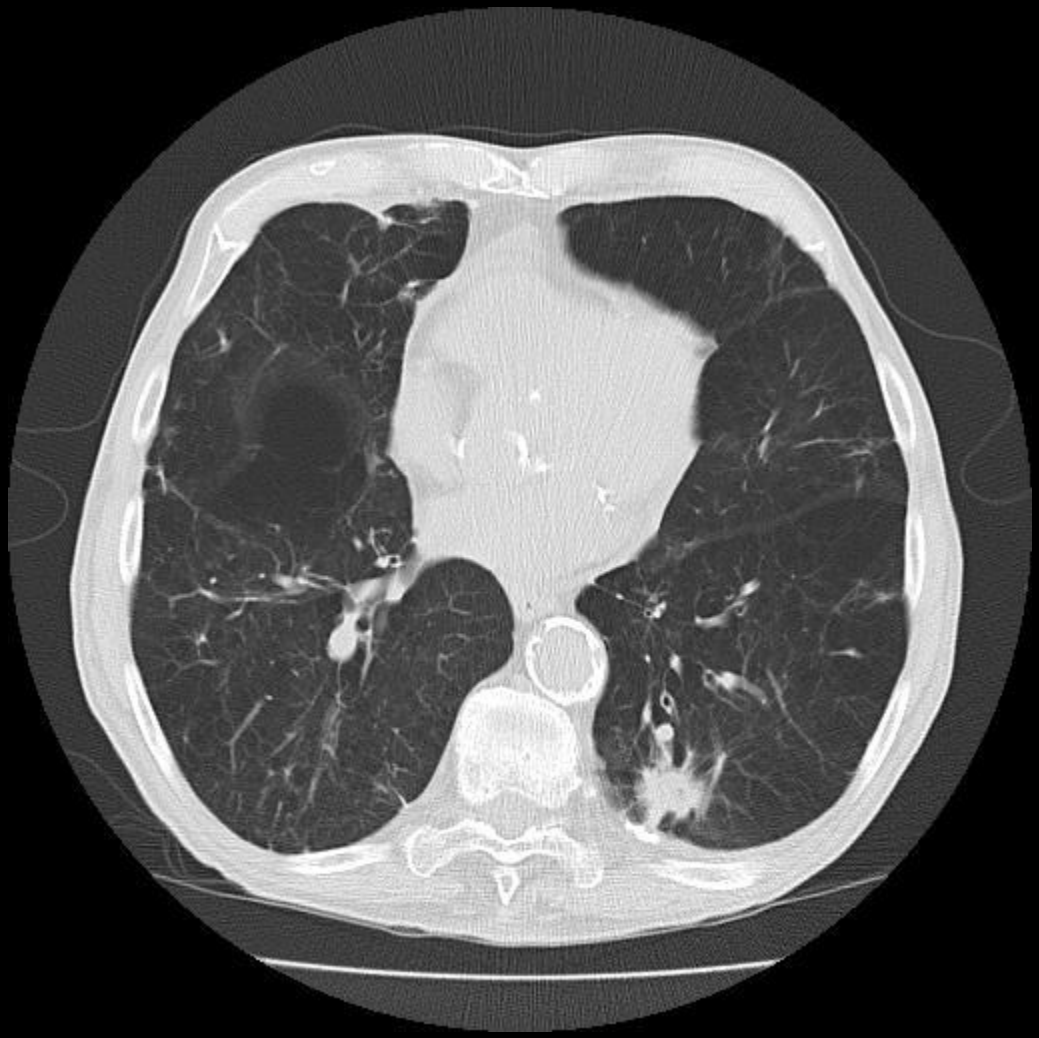
  - extremely high for spherical nodules
  - threshold for calling increased volume: 15%

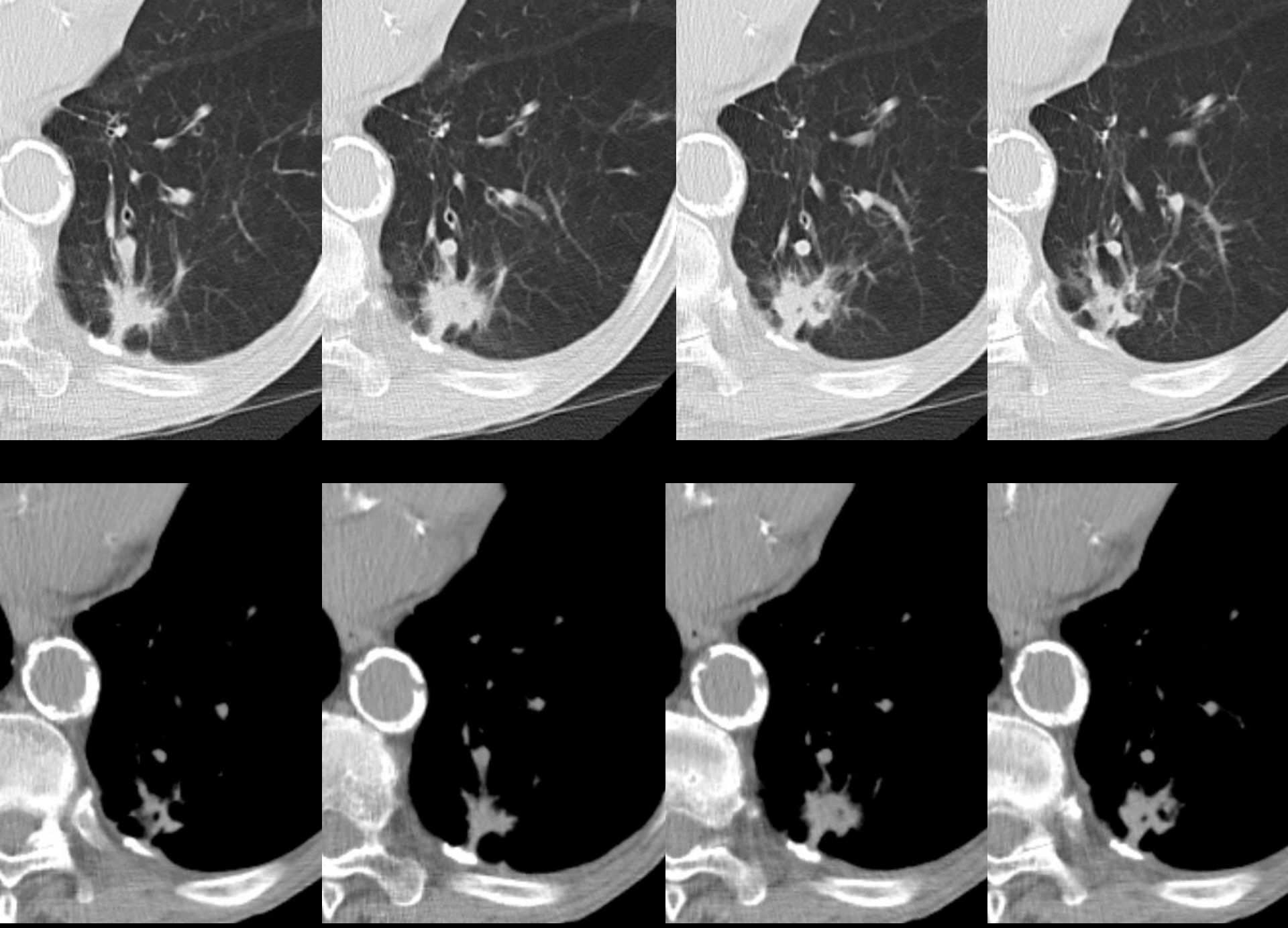
  - decreased for nonspherical nodules
  - threshold for calling increased volume: 30%

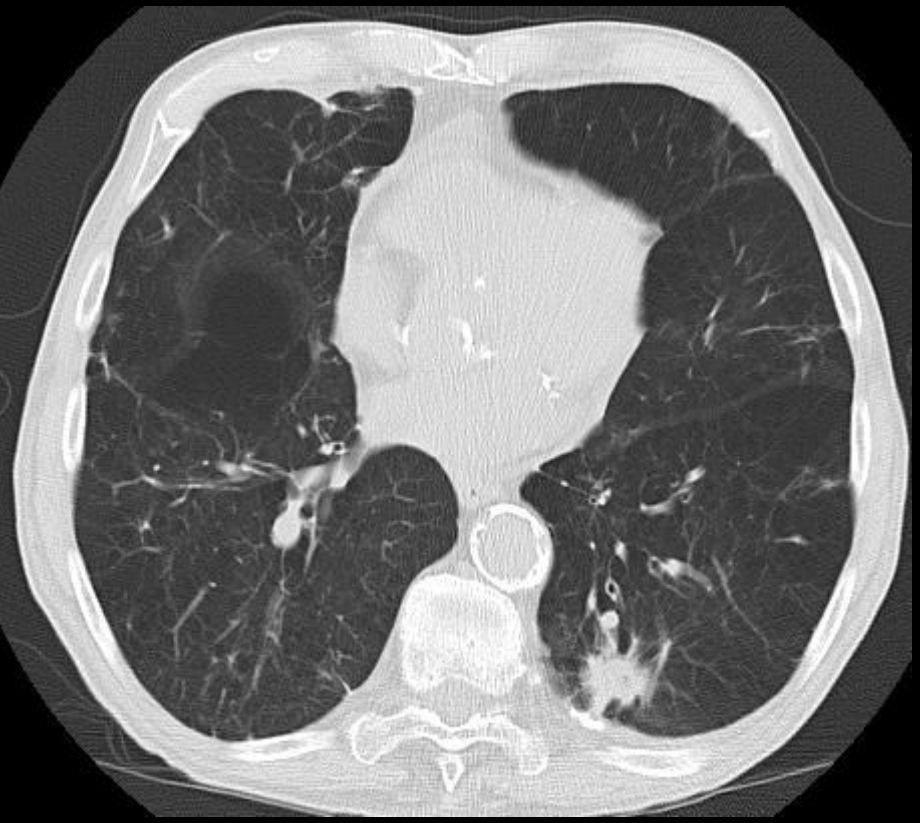
nodule follow up

- solid lesions $< \sim 5$ mm
  - no follow-up
- solid lesions 5 – 10 (15?) mm
  - surveillance of growth
- solid lesions > 10 (15?) mm
  - immediate bx?

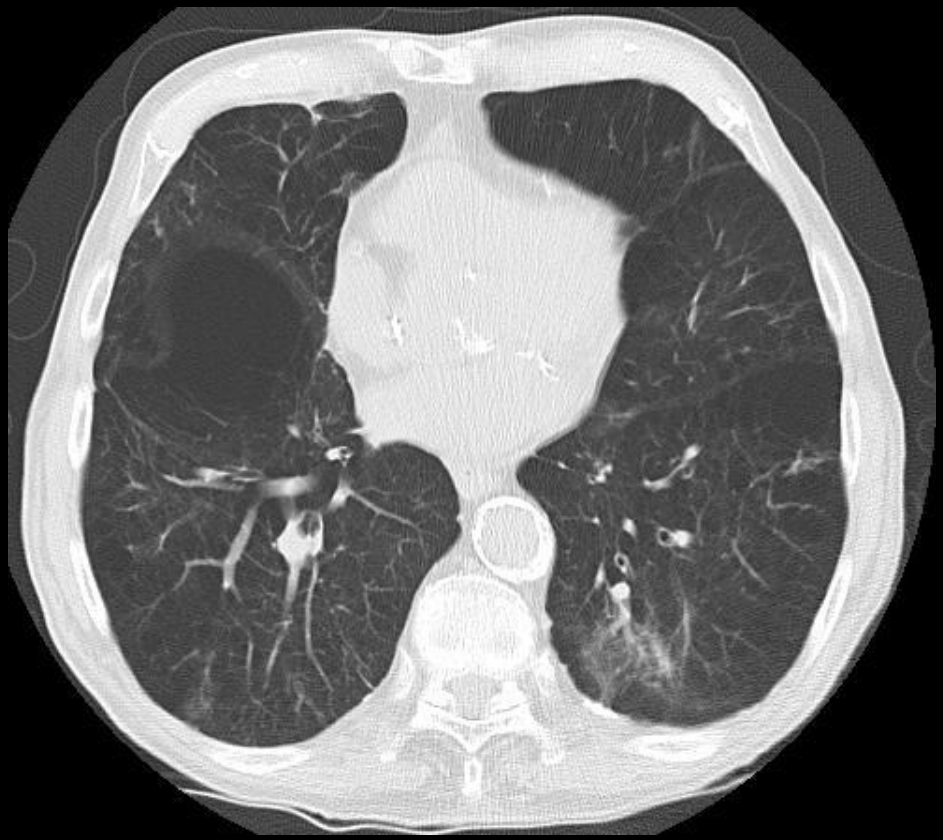
example: screen-detected nodule





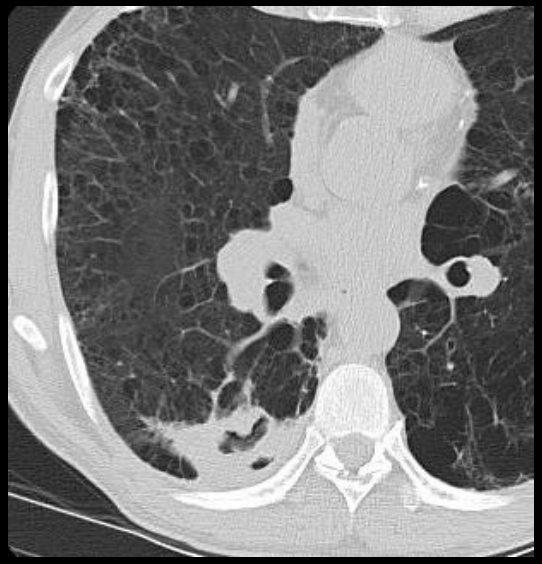


baseline



3 months follow up

examples: screen-detected nodules



example: lung nodules

CT for hemoptysis

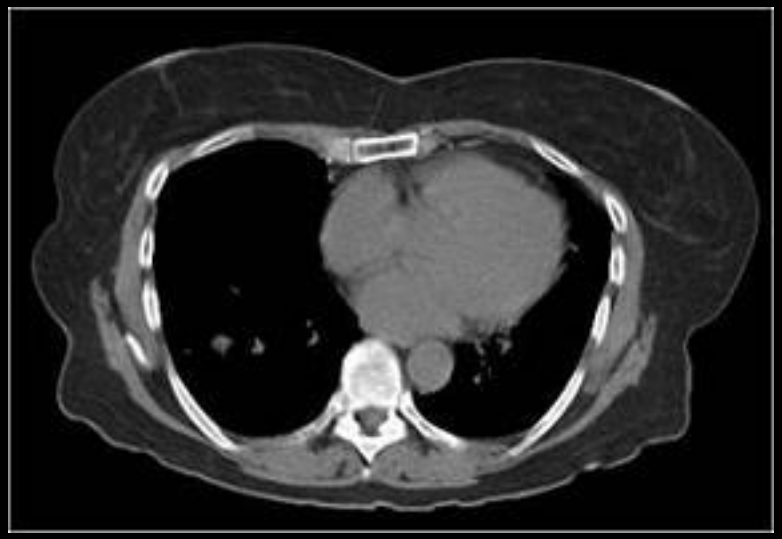
bx planning CT

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”*

U.S. Preventive Services Task Force

- 2004
- 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.

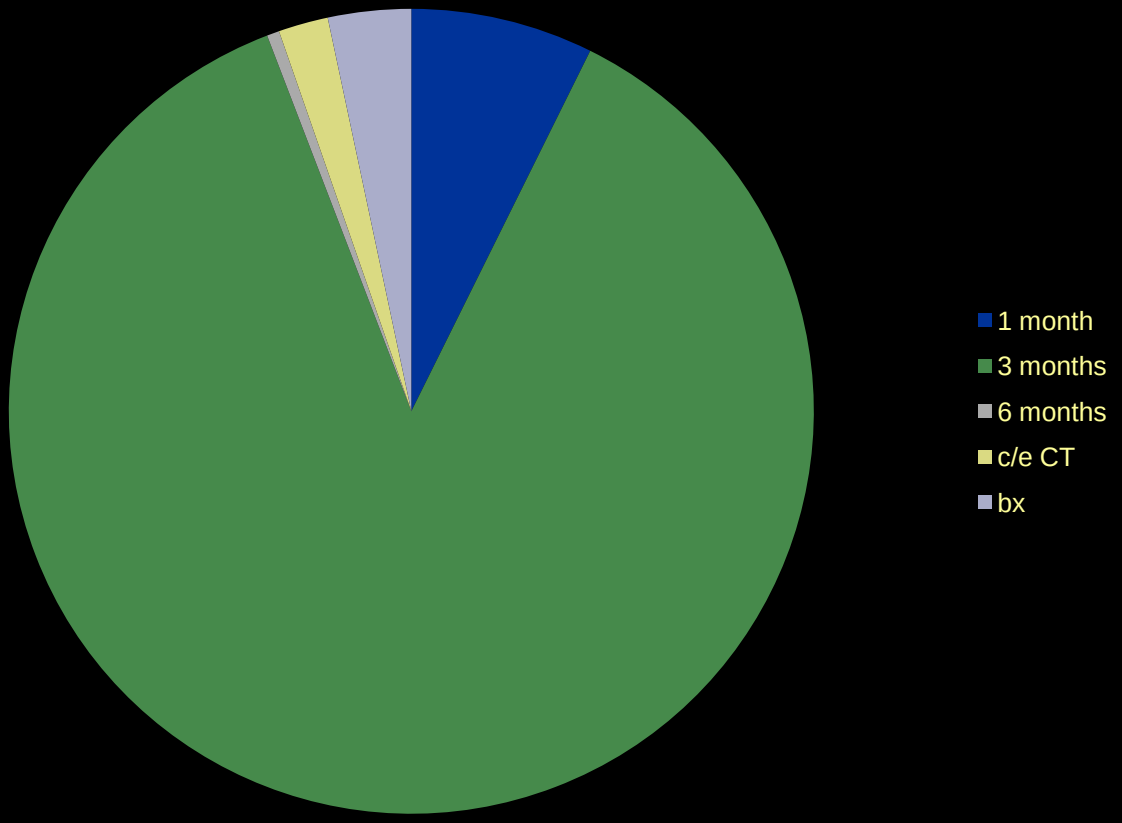
U.S. Preventive Services Task Force

- The USPSTF found fair evidence that screening with LDCT, chest radiographs, or sputu… cytology can de… cancer a… th…
- howeve… …und n…

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

…sive …gnostic testing …e possibility of a high number of false-positive tests in certain populations, there is potential for significant harms from screening.

Screening – positive baseline



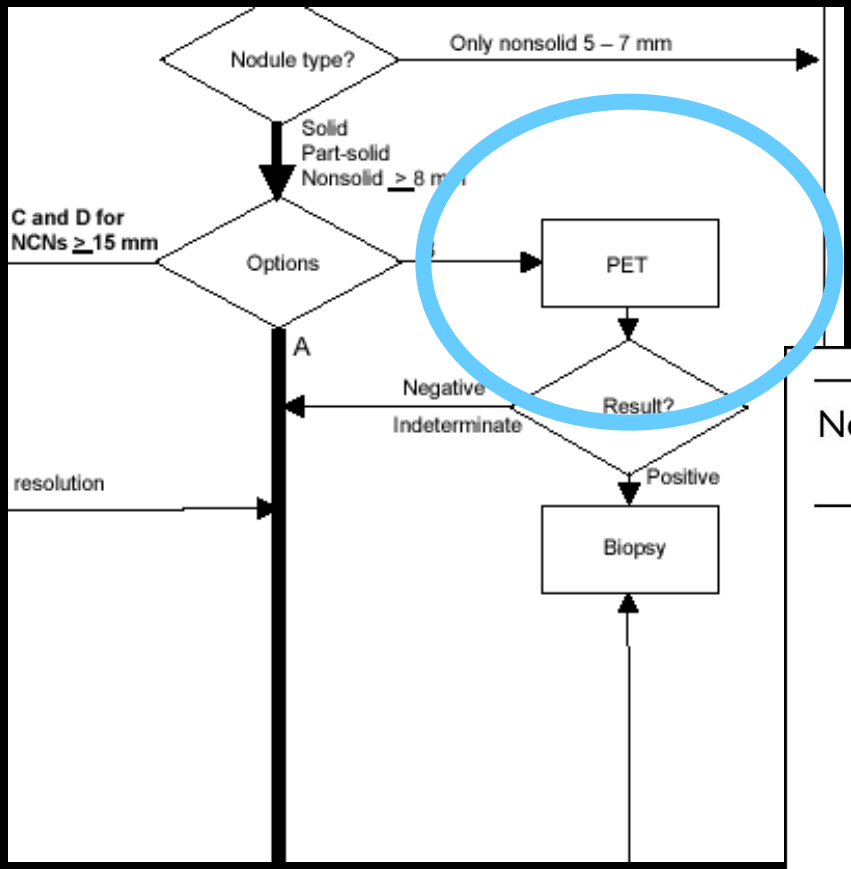
Menezes, Roberts Lung Cancer 2009

false positives

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

[Wagnetz, Roberts, et al. 2010]

PET



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

Nodule Size (mm)*	Low-Risk Patient†	
≤4	No follow-up needed§	Follo ur
>4–6	Follow-up CT at 12 mo; if unchanged, no further follow-up‖	Initia at
>6–8	Initial follow-up CT at 6–12 mo then at 18–24 mo if no change	Initia at
>8	Follow-up CT at around 3, 9, and 24 mo, dynamic contrast-enhanced CT, PET, and/or biopsy	Sam

Lung Cancer Screening

Radiation risk

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

OMA April 2010

- 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 ~ 2 million
  55-75 years old

- 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

? $ saved

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

predictive 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

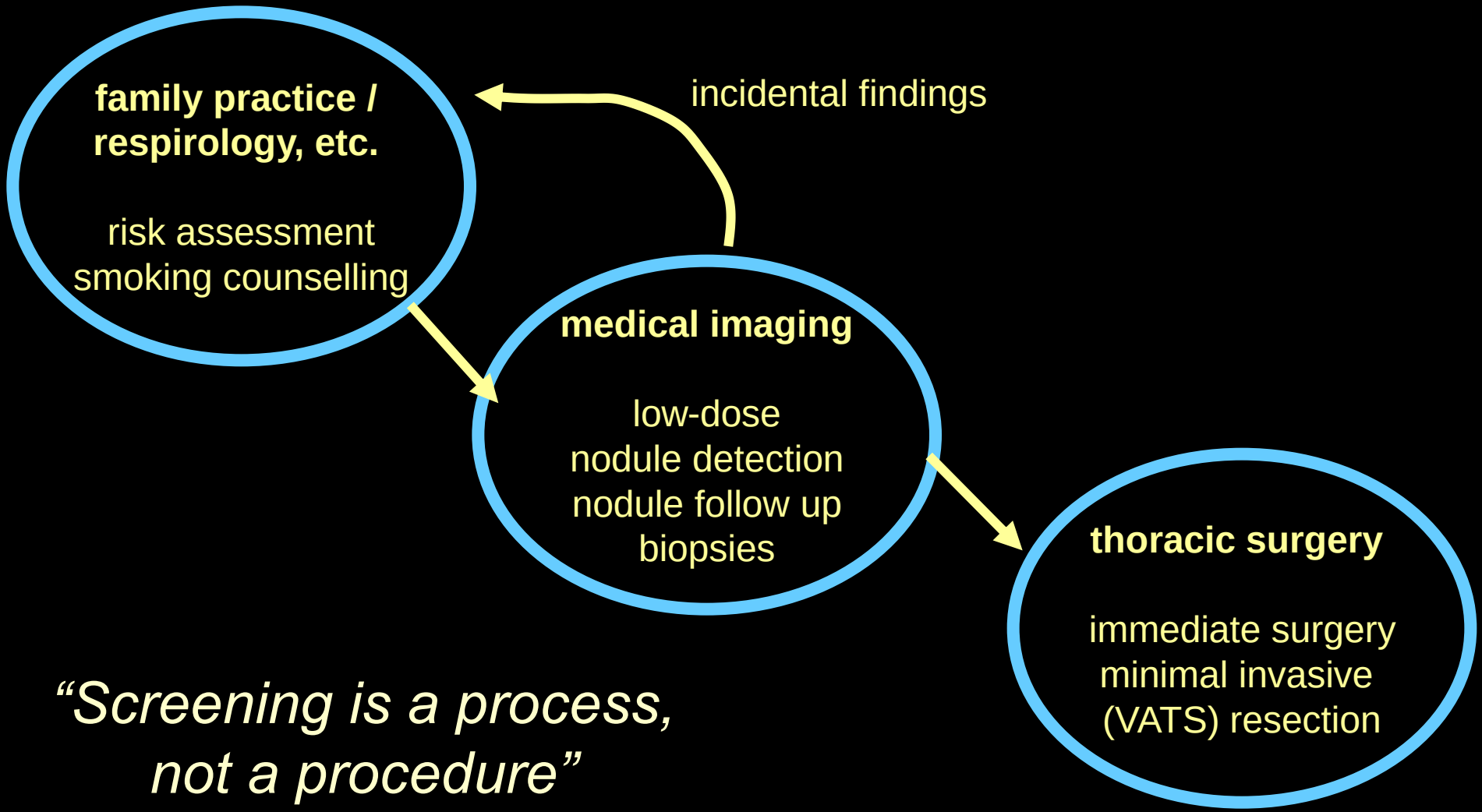
- applied to participants of the

  Pan-Canadian Early Lung Cancer Detection Study

- detection rate >2.6%

+ spirometry
+ biomarker
+ sputum anlysis

Lung Cancer Screening – network



"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