Lung Cancer Screening

nodules, cancer, mortality … and beyond

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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

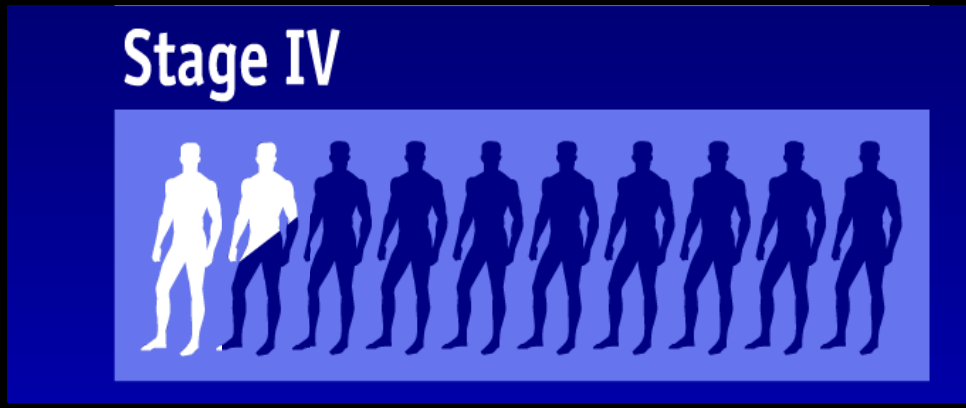
FREQUENT

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

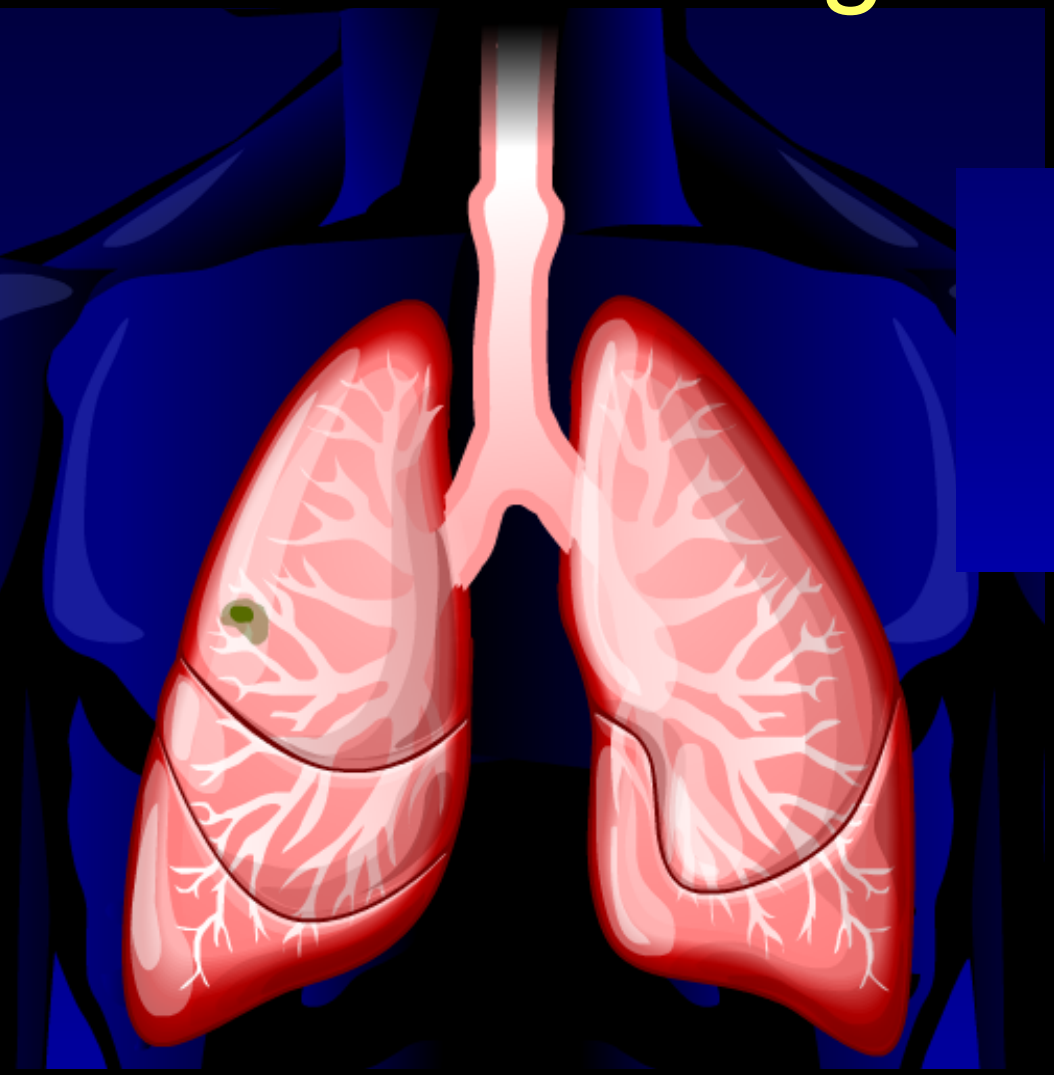
overall 5-year survival ~ 15%

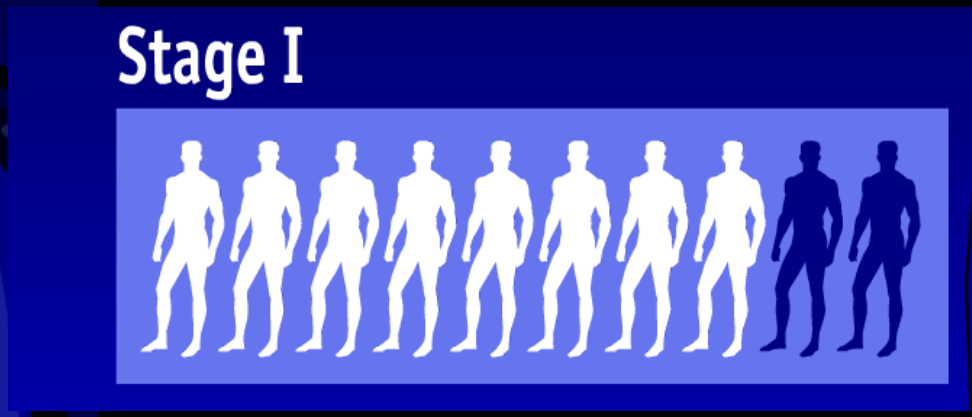
Lung Cancer



15% survival

Lung Cancer





80% survival

Screening – before Nov 2010

- impact of lung cancer

- screening CTs for lung cancer *detection*
- lung cancer stage at detection

- mortality ?

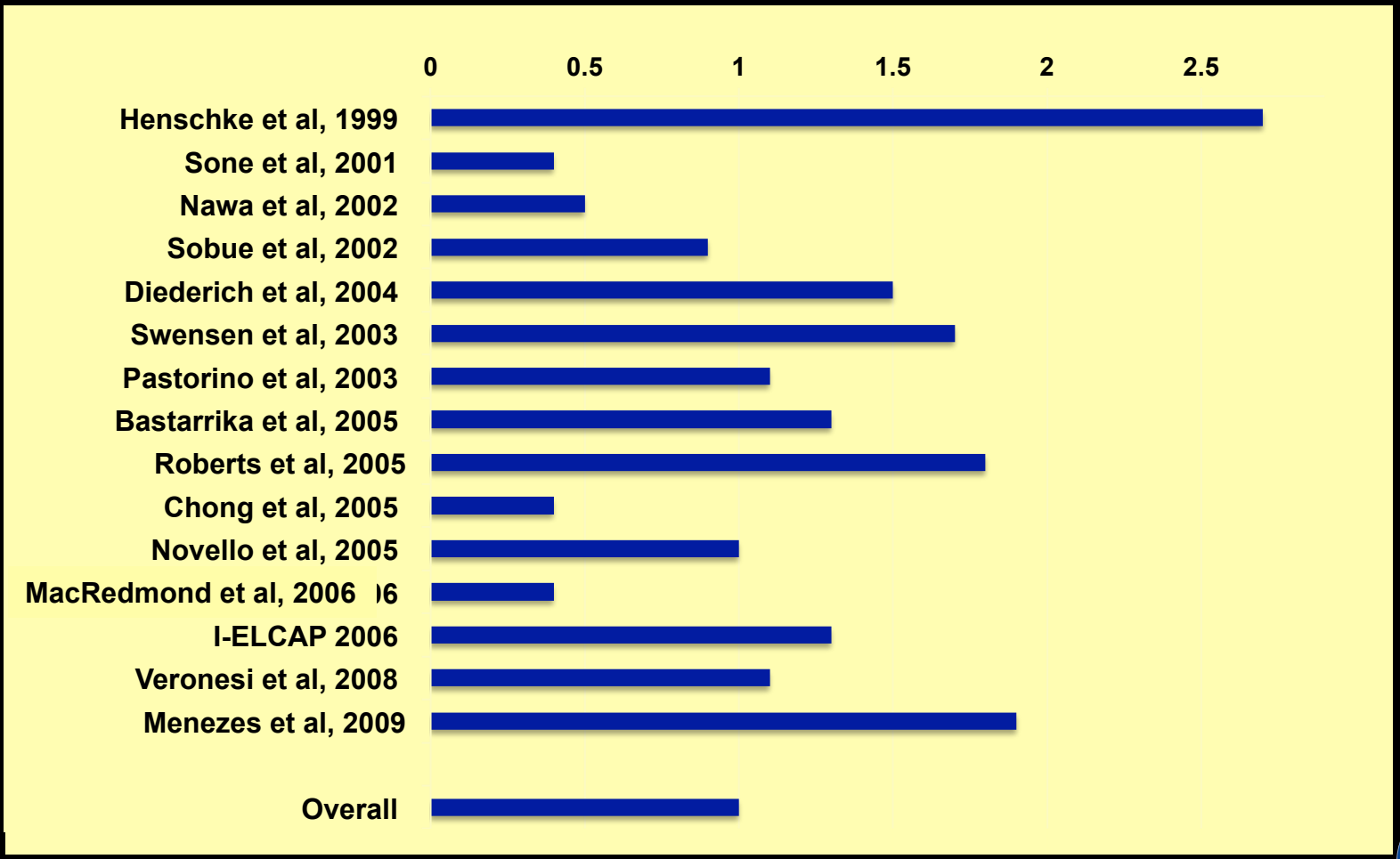
Lung Cancer Screening - Detection

high prevalence and incidence

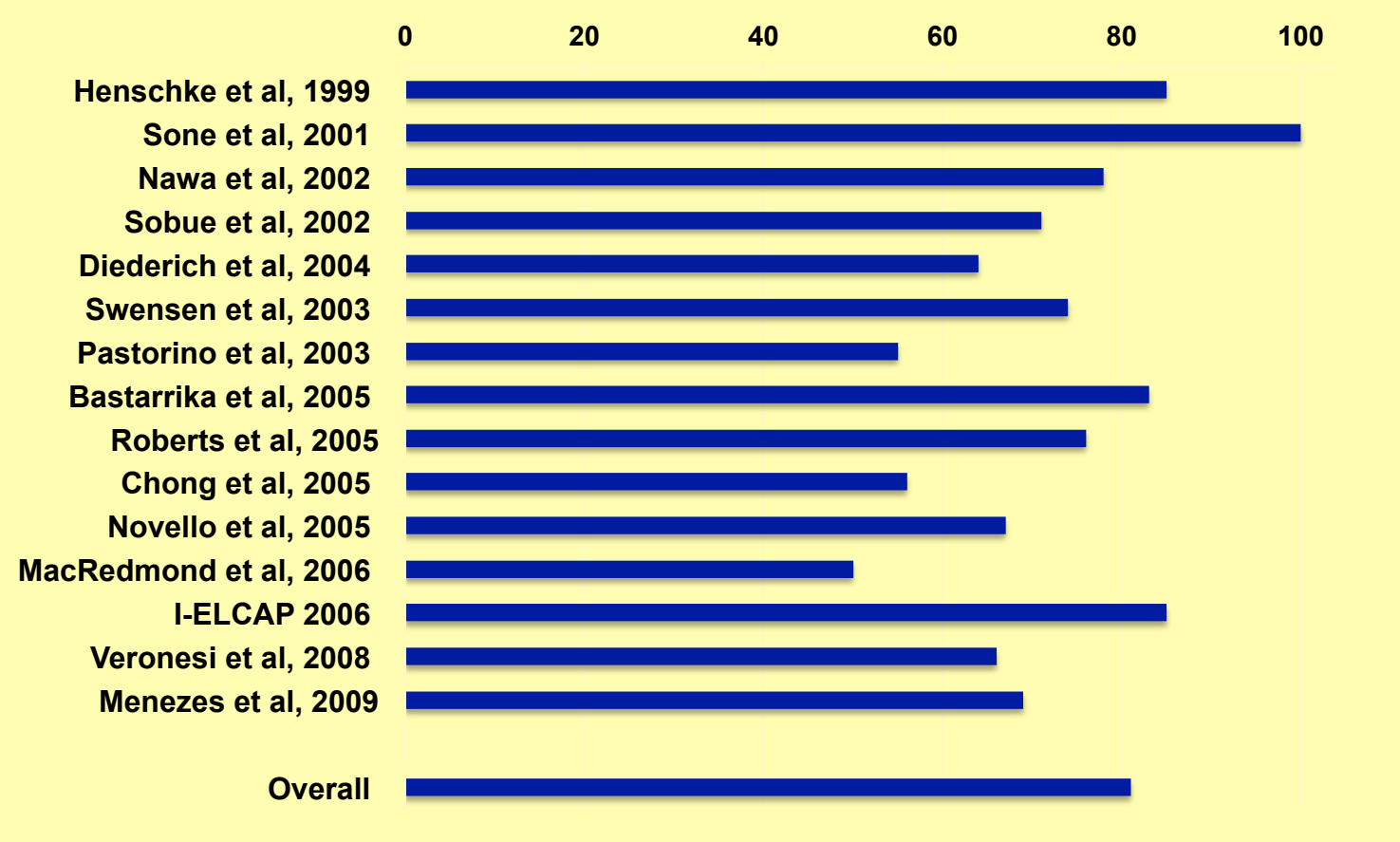
of early stage lung cancer detected at LDCT

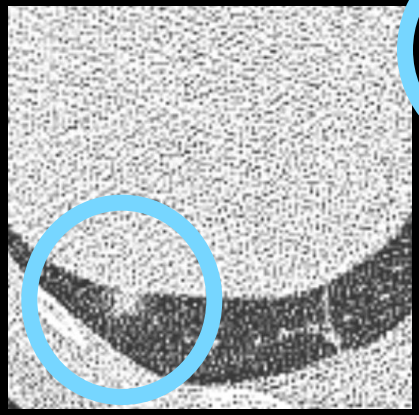
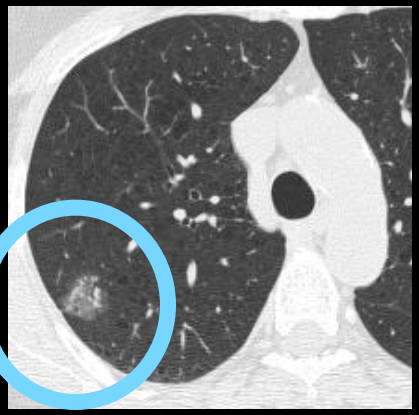
[Bellomi et al. Cancer Imaging 2009, Pastorino Brit J Cancer 2010]

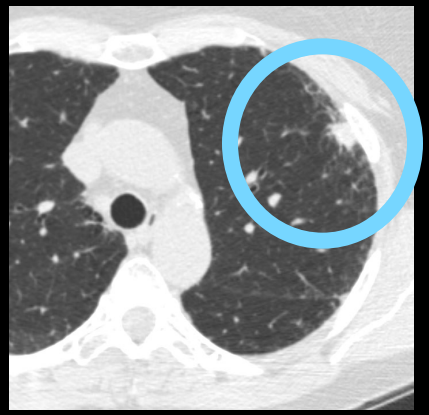
Lung cancer prevalence [%]



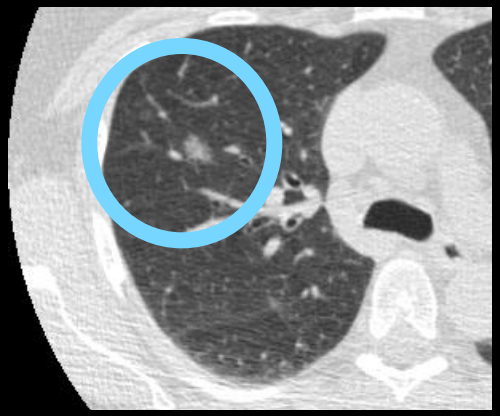
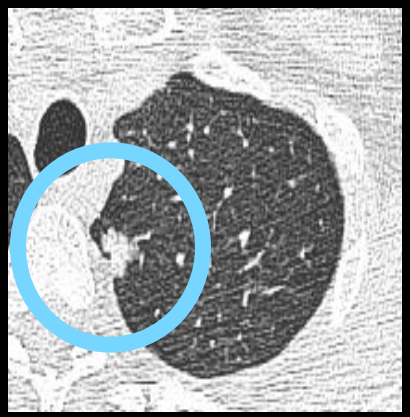
early stage lung cancers [%]





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

Screening – before Nov 2010

- impact of lung cancer

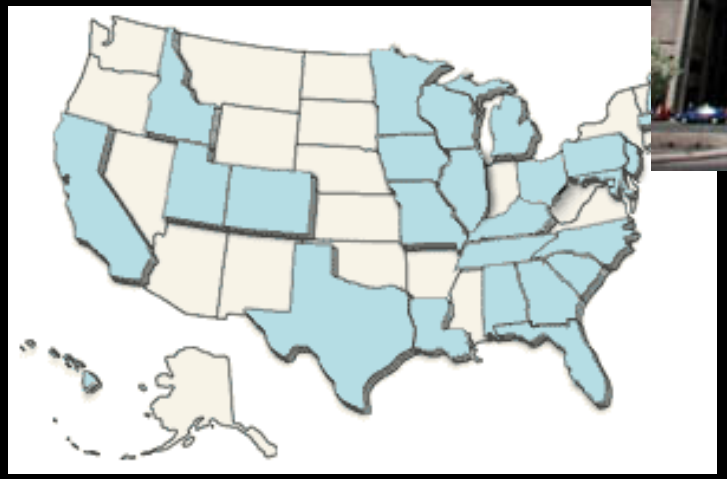
- screening CTs for lung cancer *detection*
- lung cancer stage at detection

- 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%*



Henschke et al,
New Eng J Med 2006

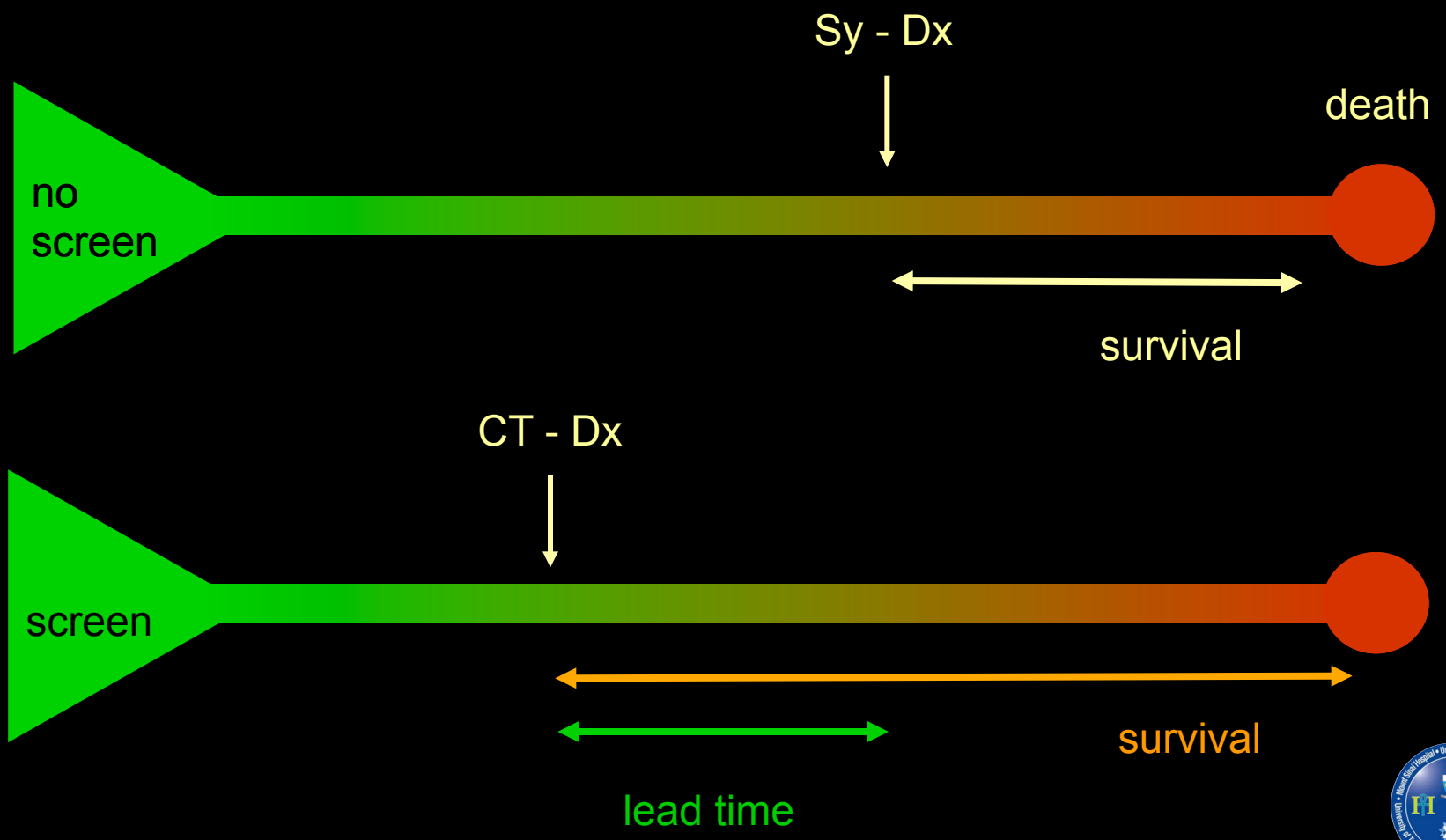
survival vs. mortality

- 10-year survival up to 92%

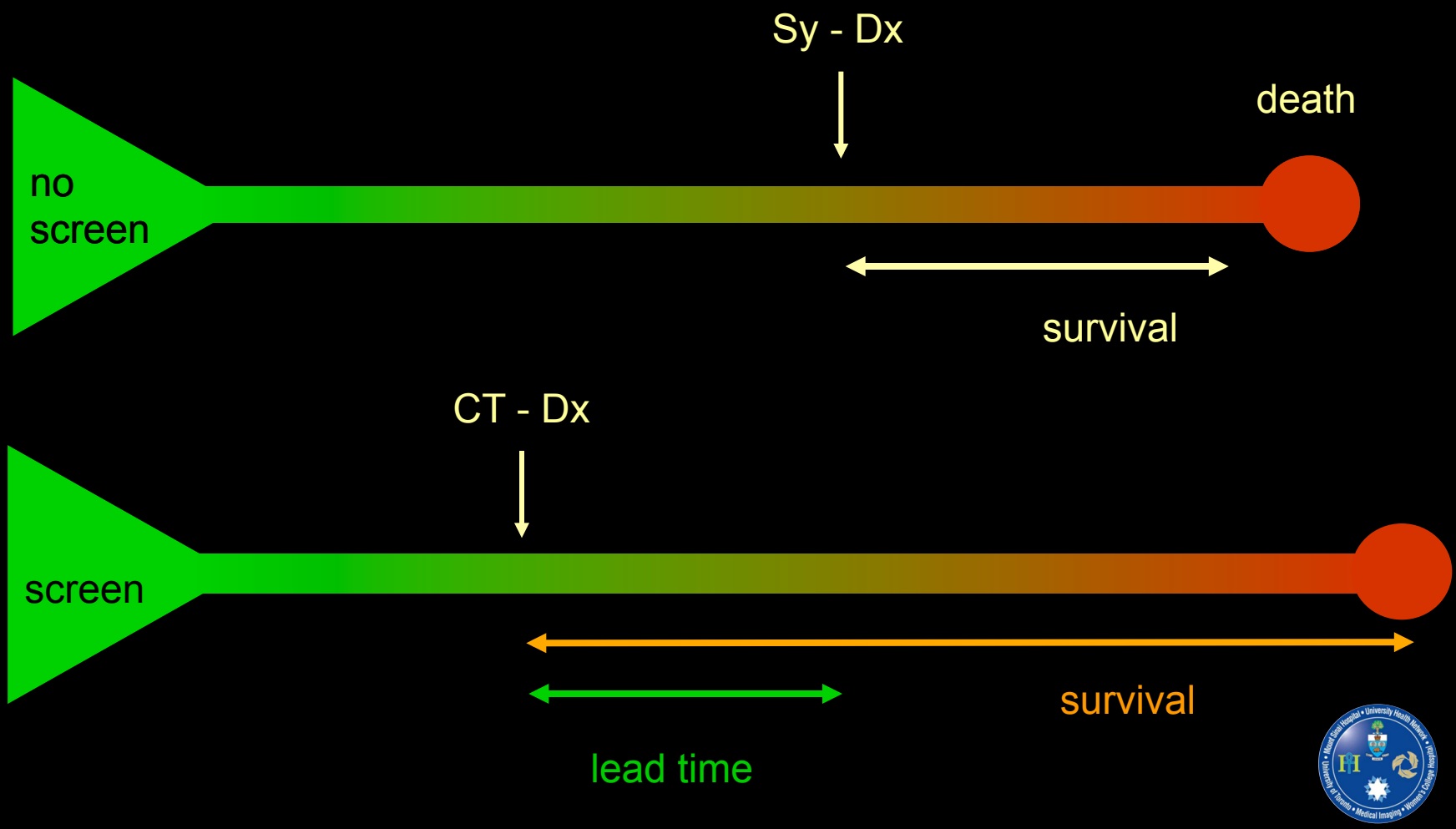
[I-ELCAP New Eng J Med 2006]

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

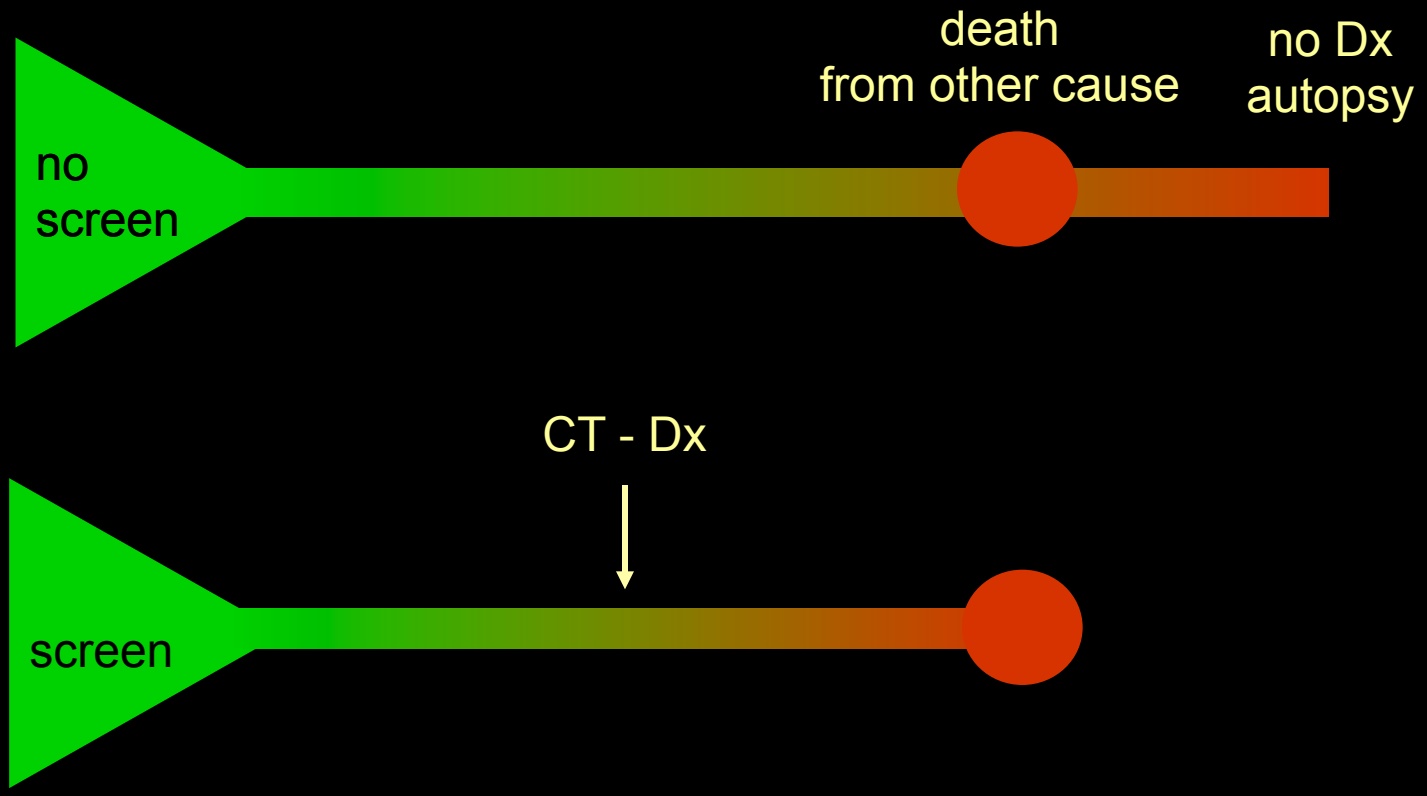
lead time bias



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

Nov 4th 2010

"Lung Cancer Screening Using LDCT Reduces Deaths"

thestar.com

CTV

CBC

- 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 scre

“ COPD, hemoptysis”
f rast-enhanced CT
r zed 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

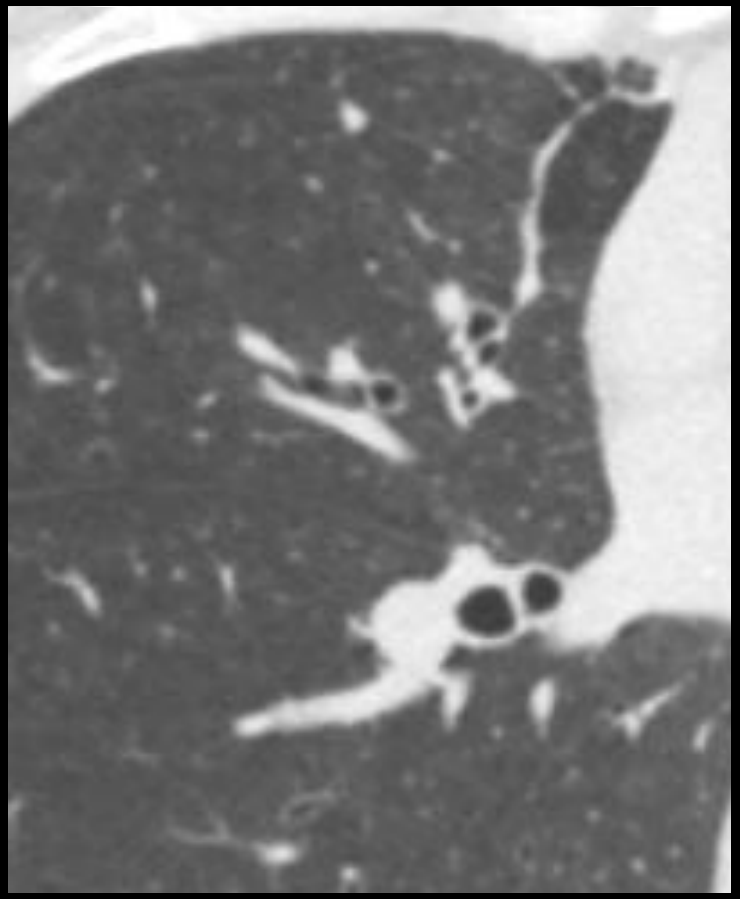
- "negative" without nodules → annual repeat
- "negative" with (small) nodules → annual repeat
- "positive" large nodules → 1 – 3 month follow up CT
  other interventions

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

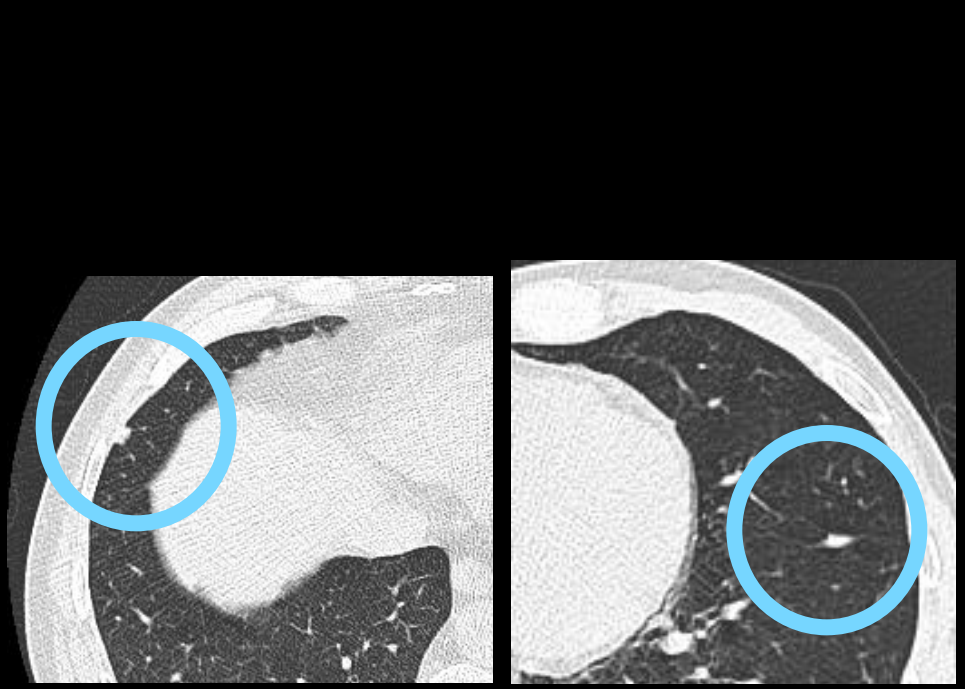
Lung Cancer Screening – nodules

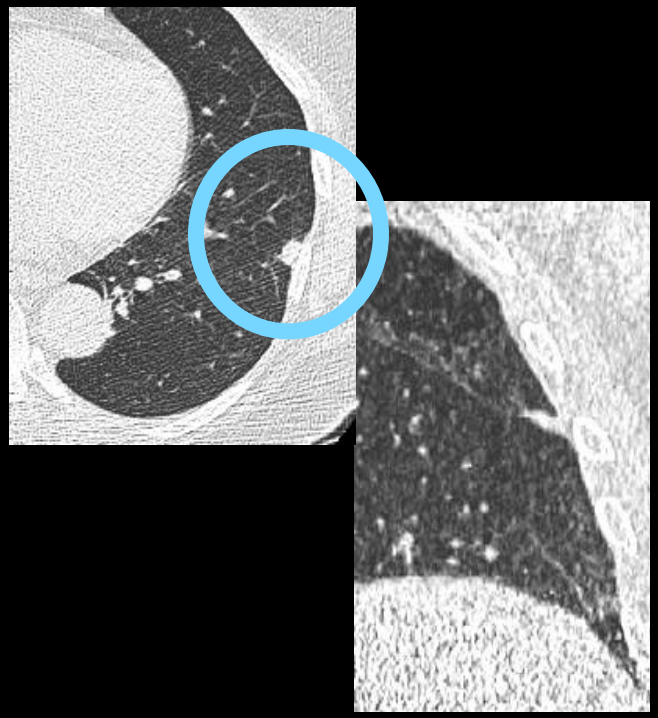
– what is NOT a nodule?



Lung Cancer Screening – nodules

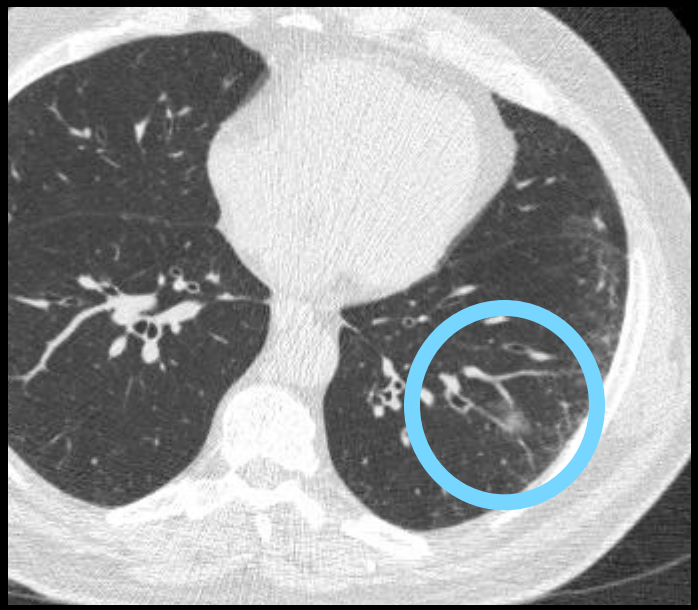
– what is NOT a nodule?

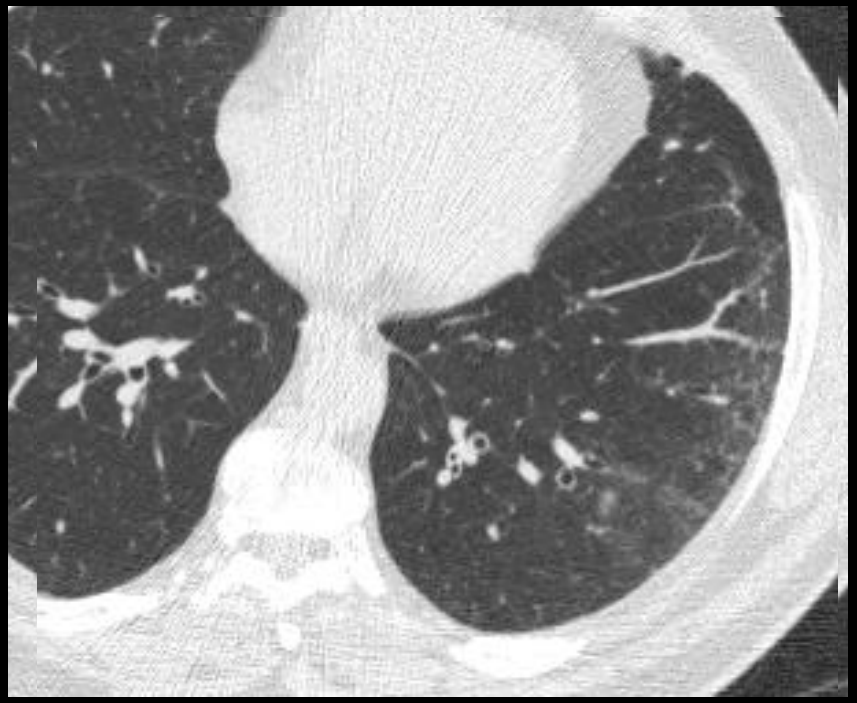




Lung Cancer Screening – nodules

– 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

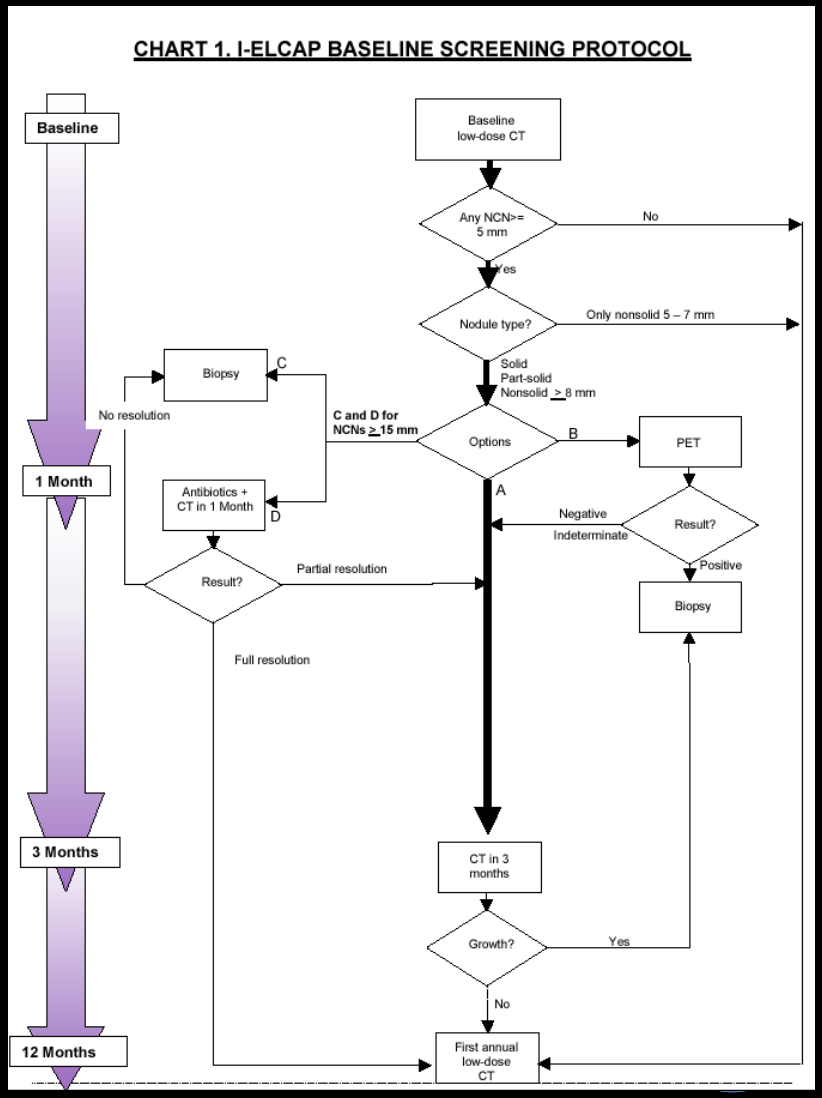
	definition	%
ELCAP *Lancet 1999*	any size	23.3
Italian SS *Lancet 2003*	6 mm	29
LSS (NCI) *Chest 2004*	4 mm	20.5
Mayo *Radiology 2005*	any	51
Toronto (n=1000) *Can Ass Rad J 2007*	5 mm	25.7
Toronto (n=3352) *Lung Cancer 2009*	5 mm	18
NLST *N Eng J Med 2011*	4 mm	27.3

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*

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

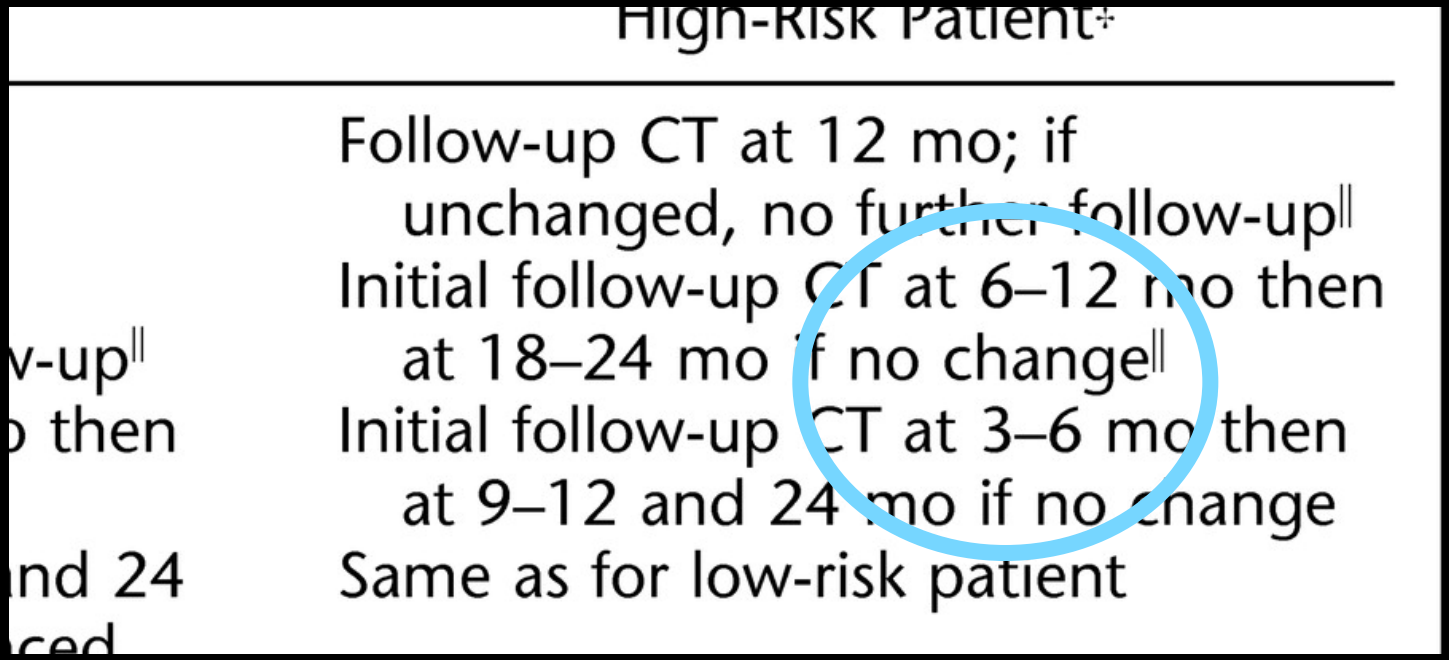
Lung Cancer Screening – nodules

- 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*
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‖
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 < ~ 5 mm
  - "negative", no follow up

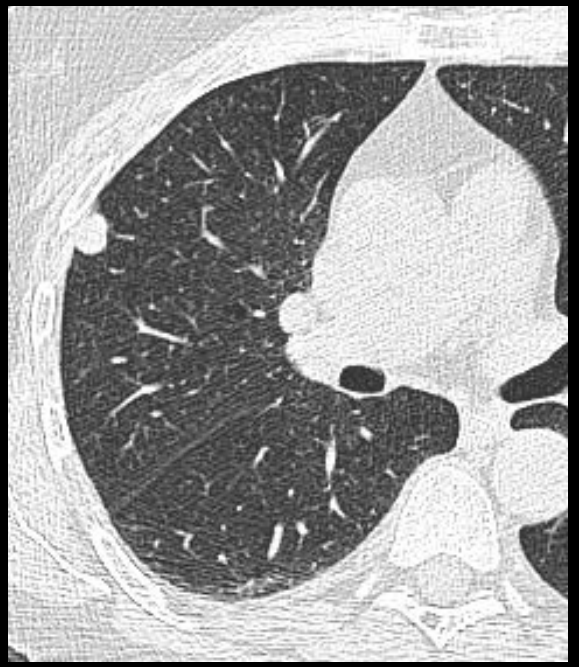
→ annual repeat

nodule follow up

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

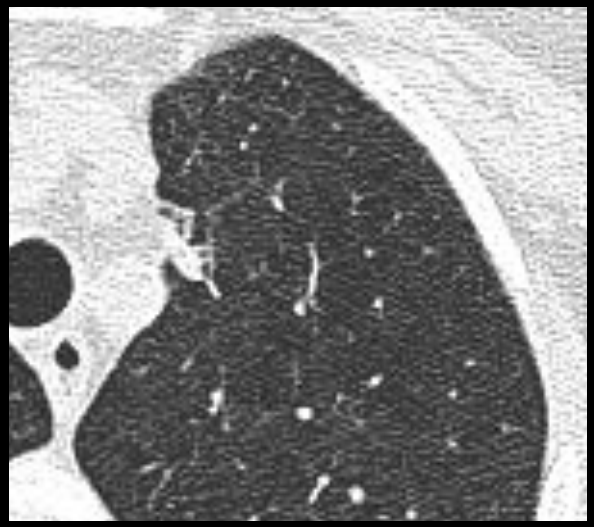
- solid lesions 5 – 10 mm
  - surveillance of growth
  - doubling time 30 – 360 = malignant

3 months

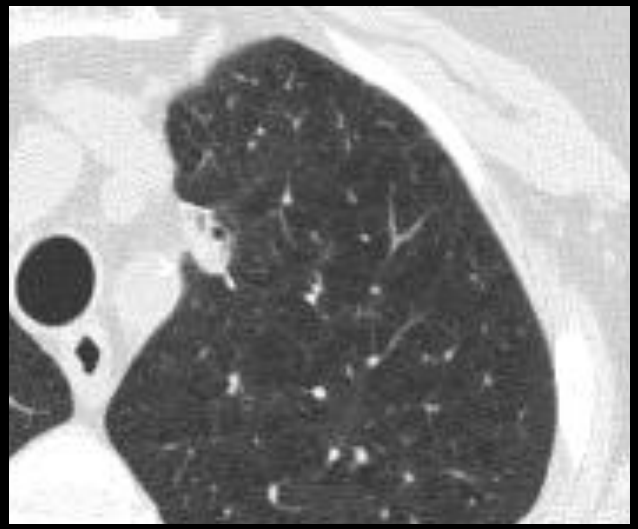


doubling time 72 days

combined small cell-large cell neuroendocrine carcinoma



3 months



mucinous adenocarcinoma

nodule follow up

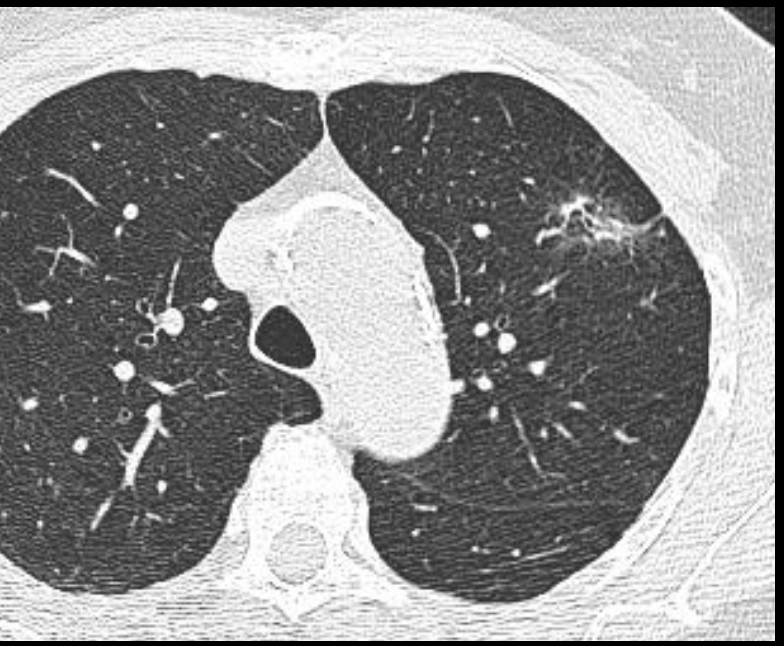
- solid lesions < ~ 5 mm
  - no follow up
- solid lesions 5 – 10 mm
  - surveillance of growth

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

3 months

same size, higher density

adenocarcinoma



3 months

measurement?

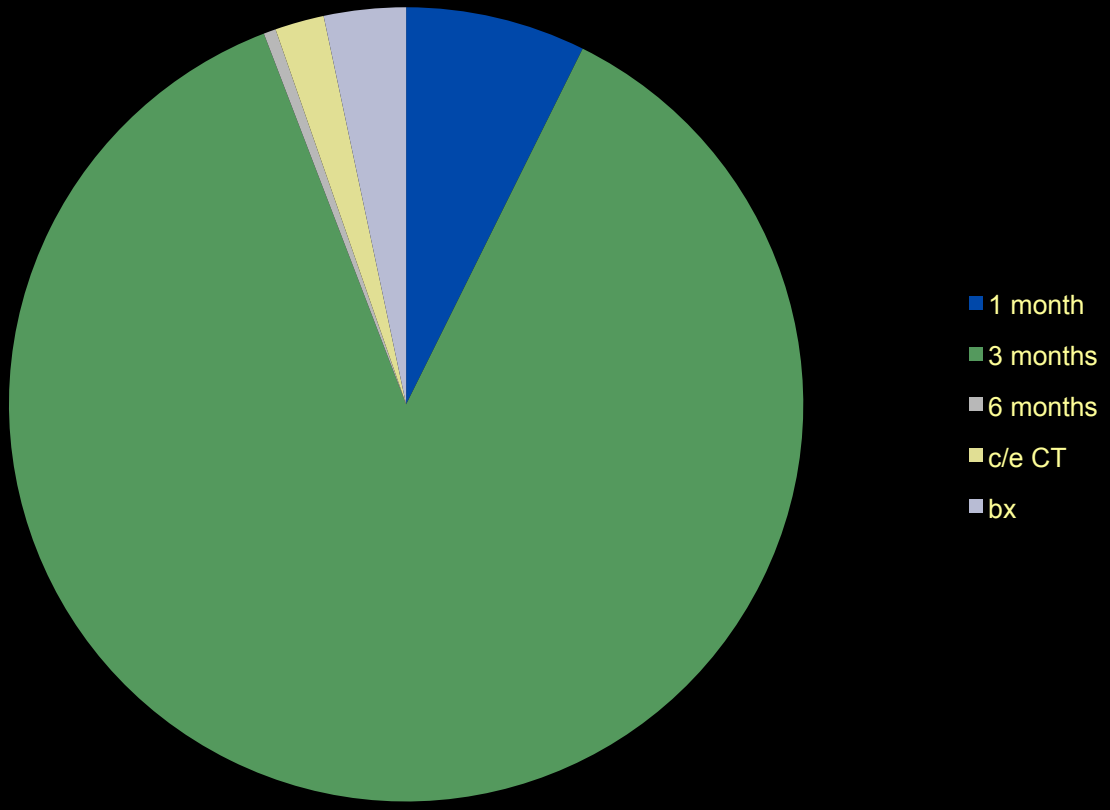
adenocarcinoma

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

Wagnetz, Roberts, et al; AJR in press, 2011

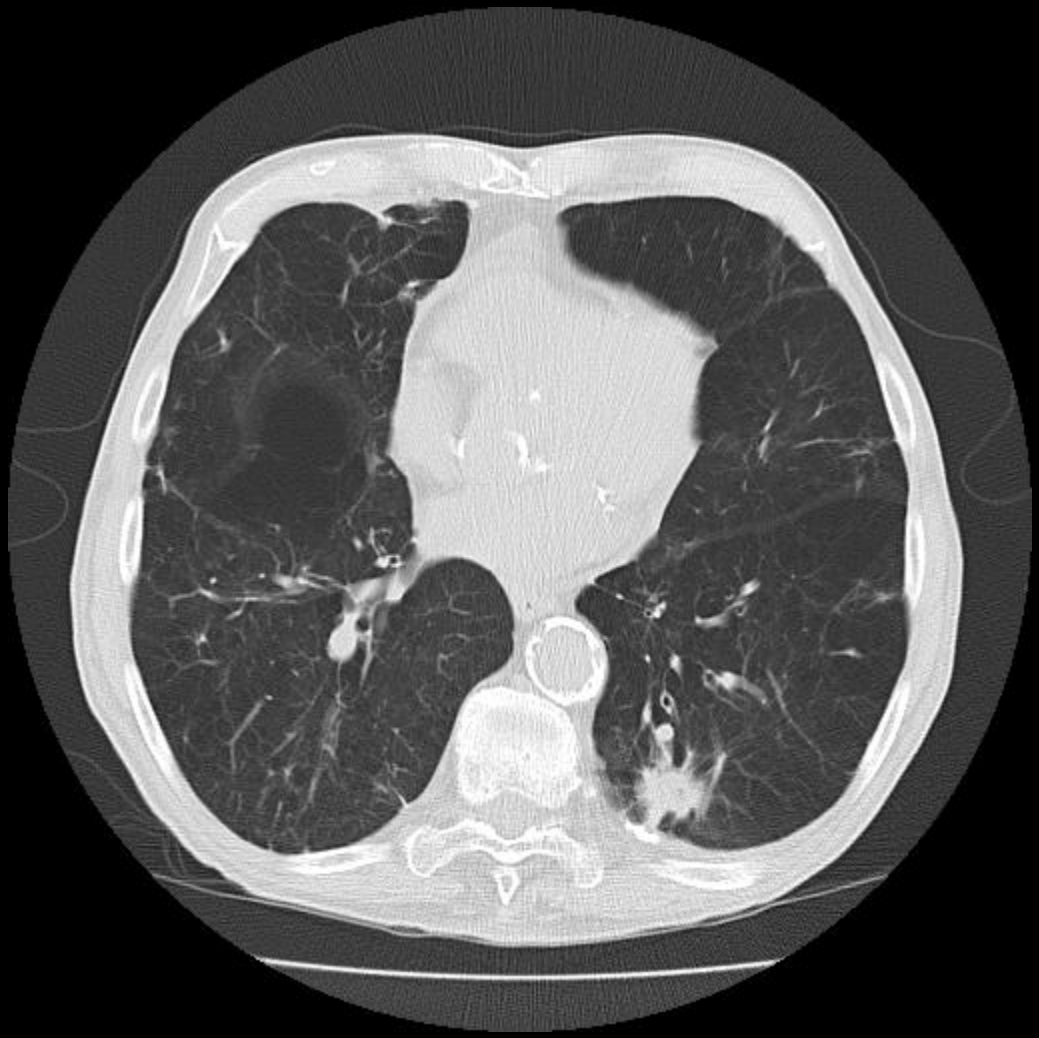
nodule follow up

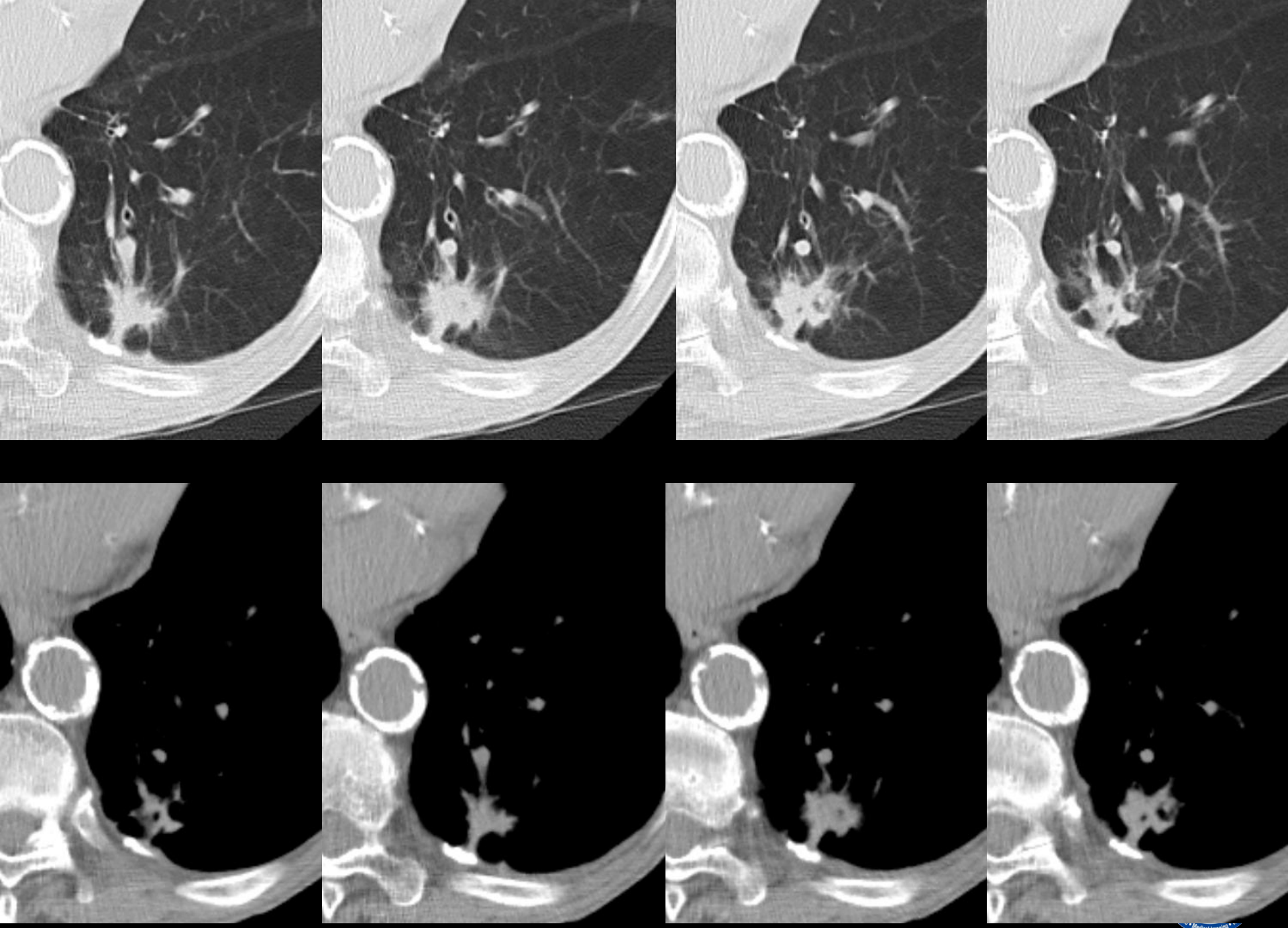
- solid lesions < ~ 5 mm
  - no follow-up

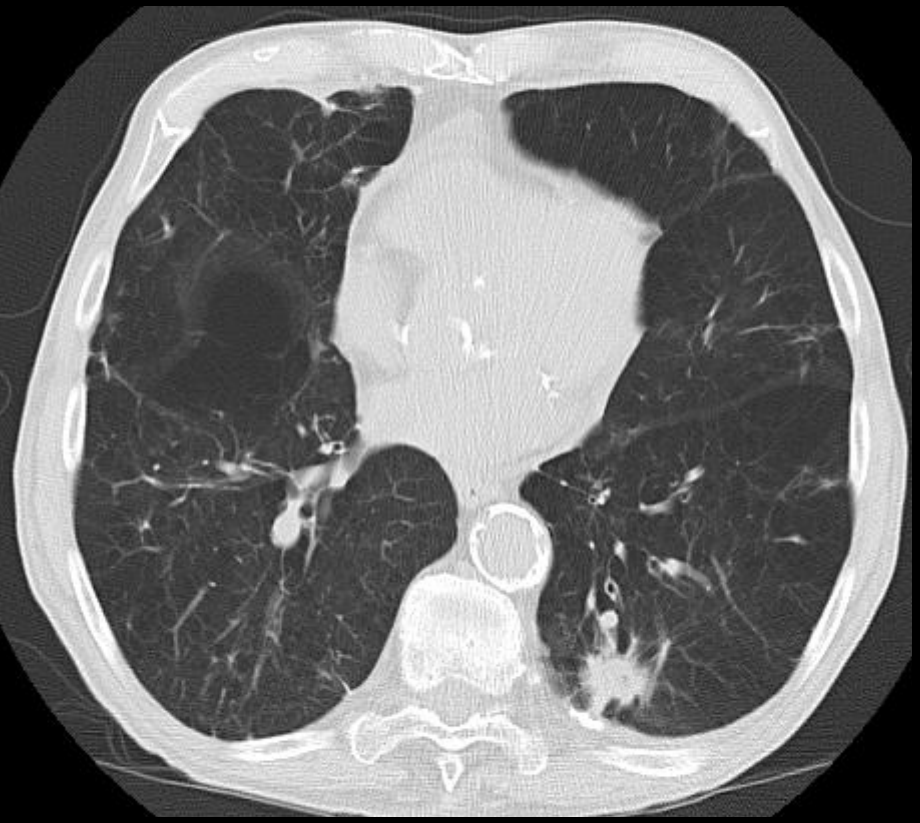
- solid lesions 5 – 10 (15?) mm
  - surveillance of growth

- solid lesions > 10 (15?) mm
  - immediate bx?

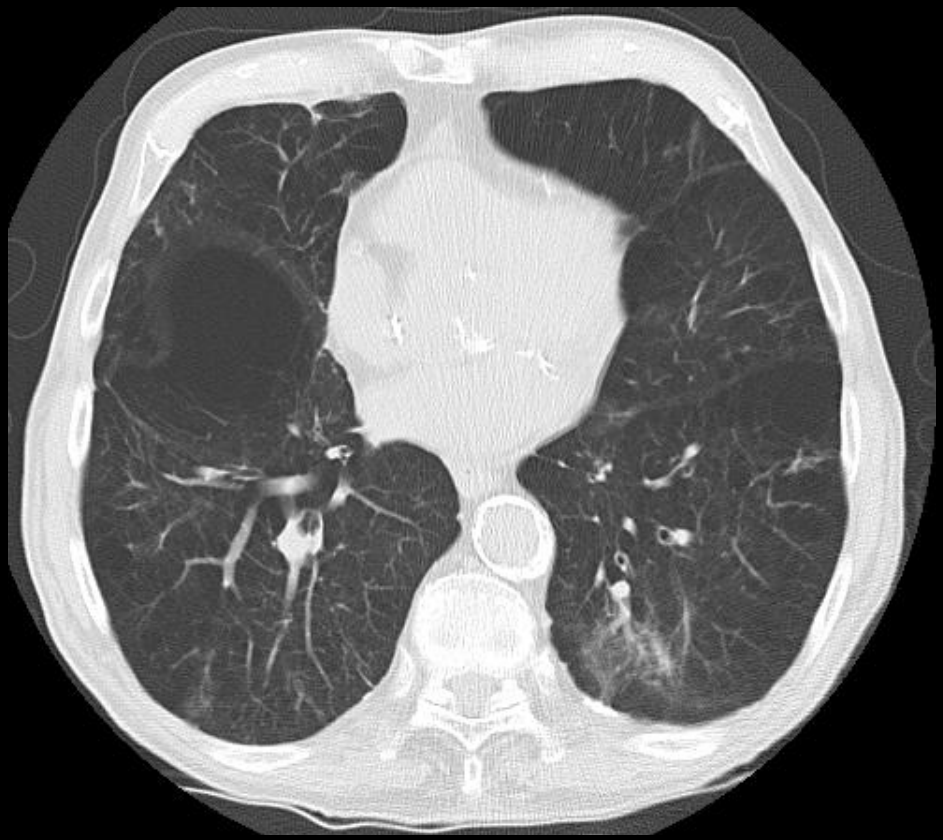
example: screen-detected nodule



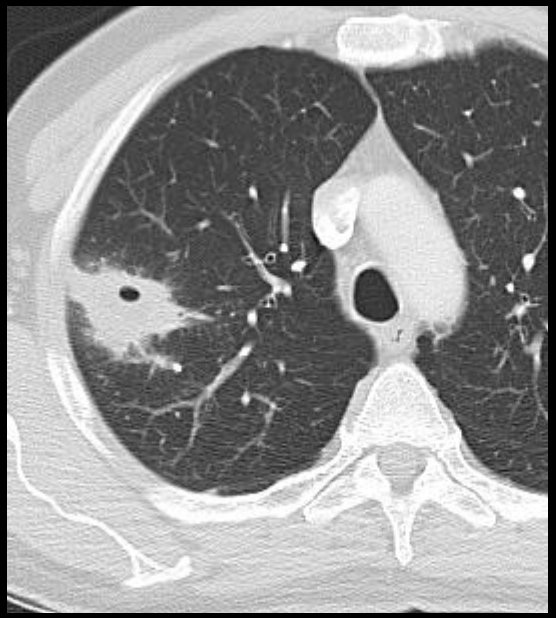


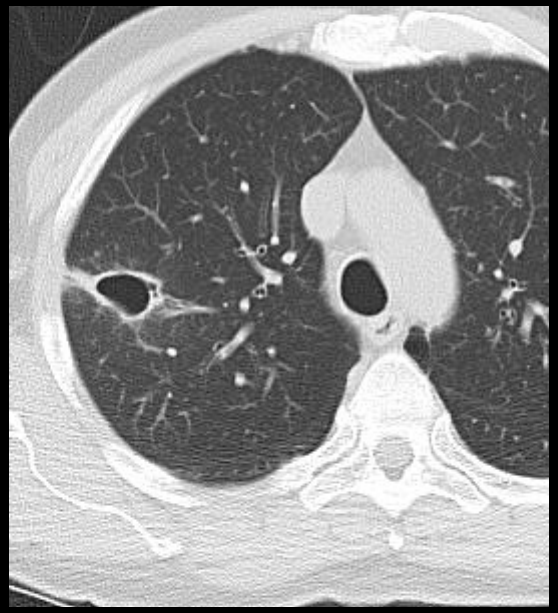


baseline

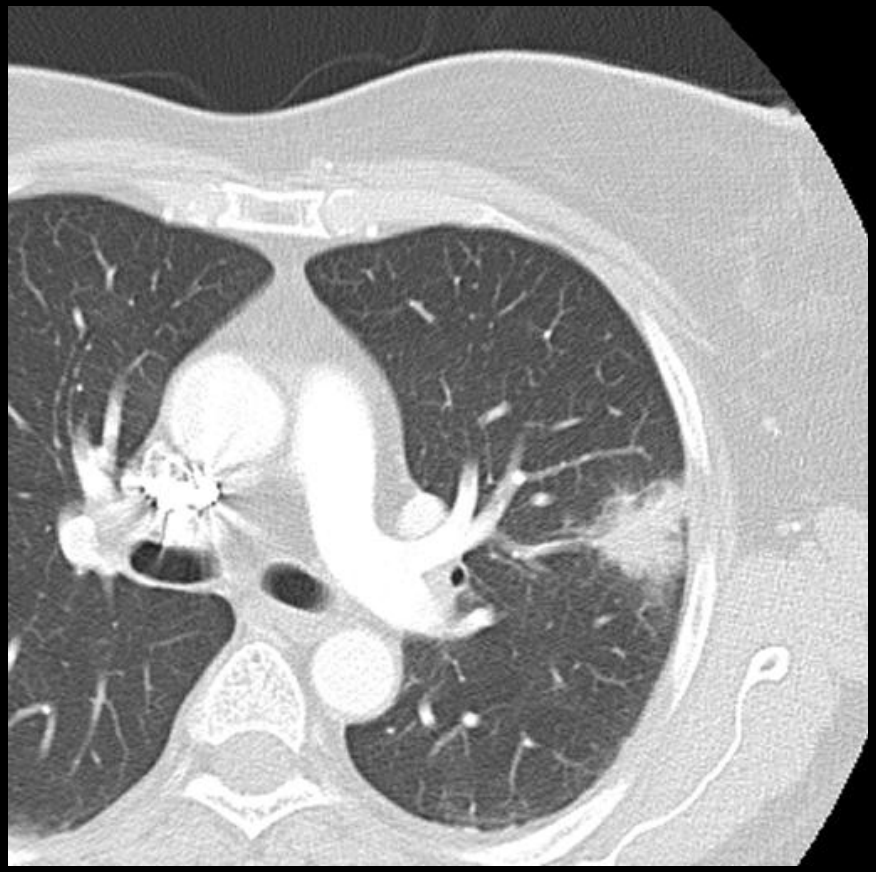


3 months follow up

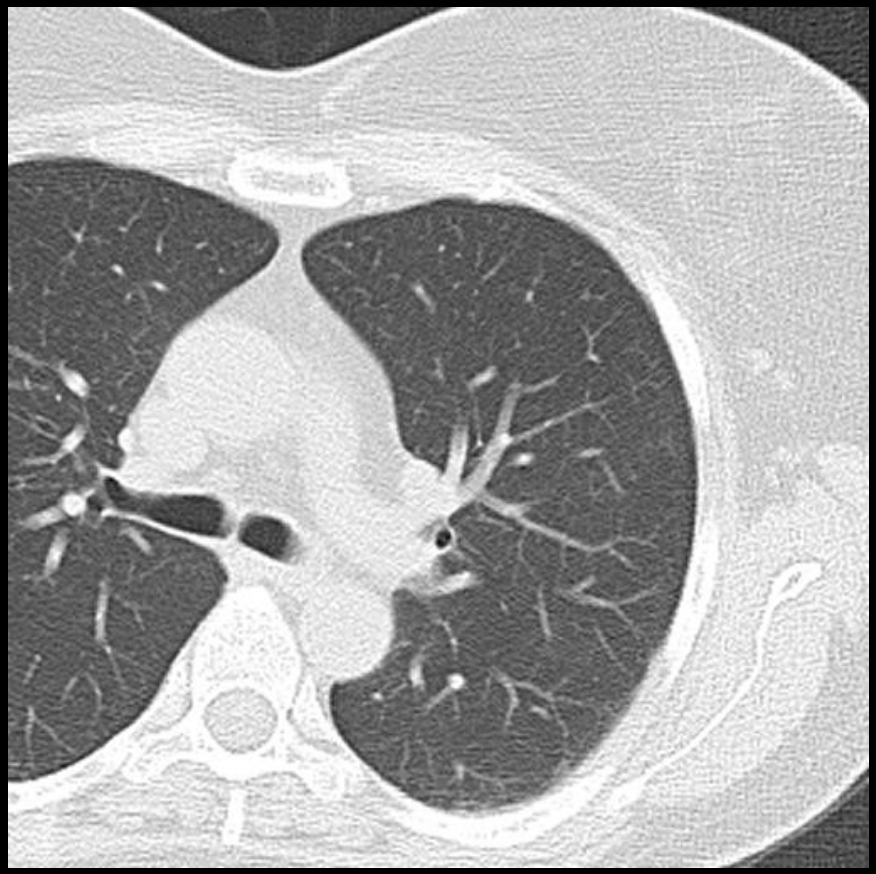




bx planning CT



June 23rd

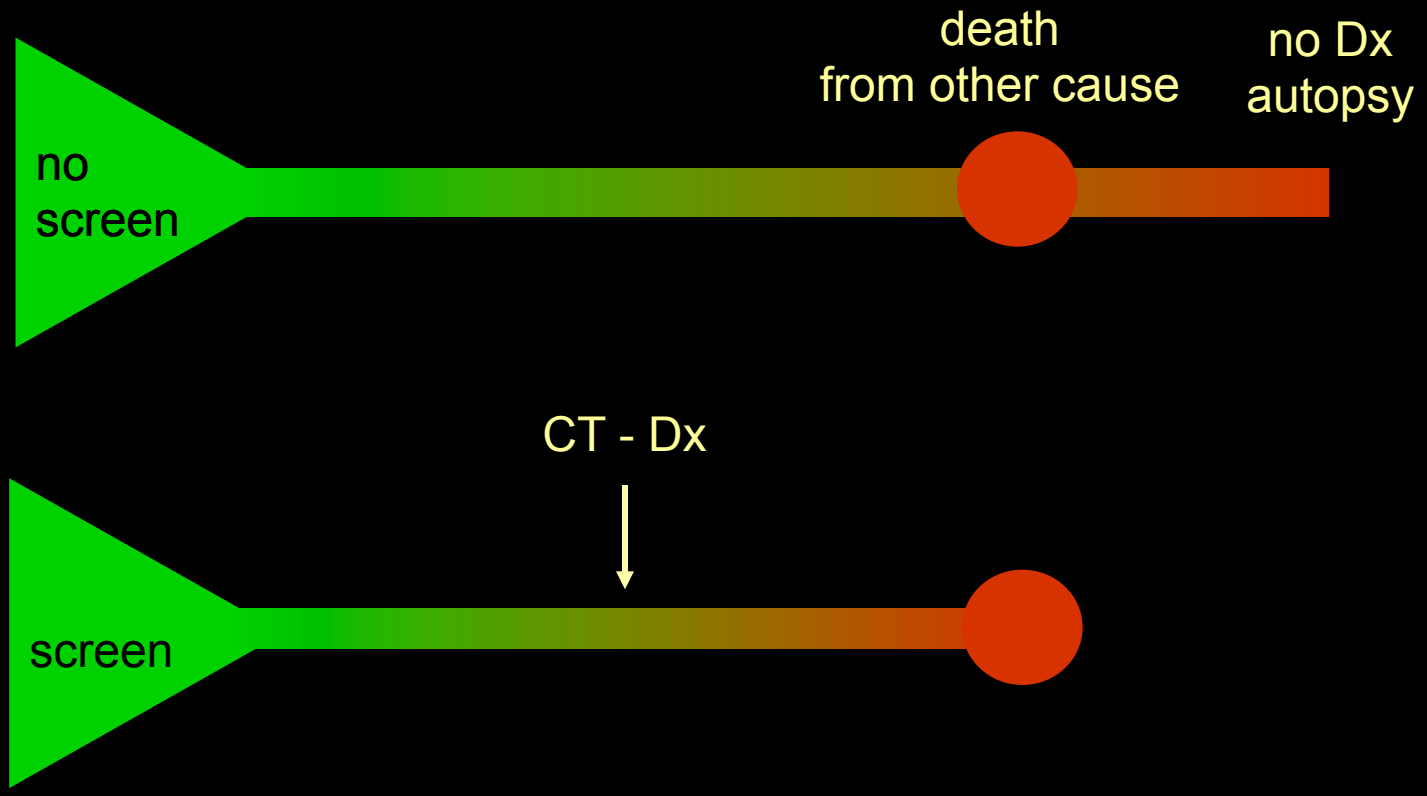


July 29th

Screening – beyond mortality

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

overdiagnosis bias



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

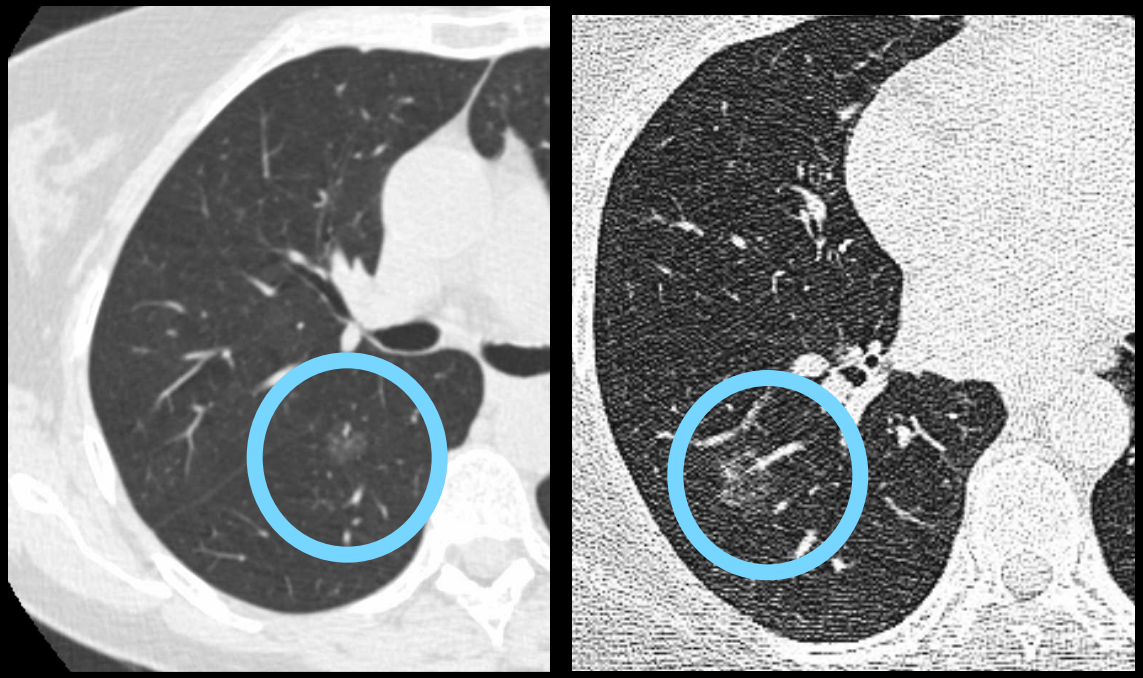
overdiagnosis bias?

- 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

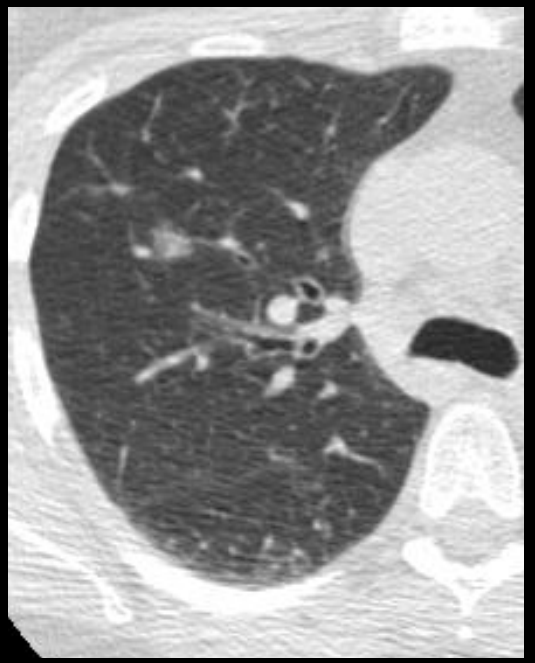
overdiagnosis bias ?

overdiagnosis bias

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

overdiagnosis bias ?

3 months

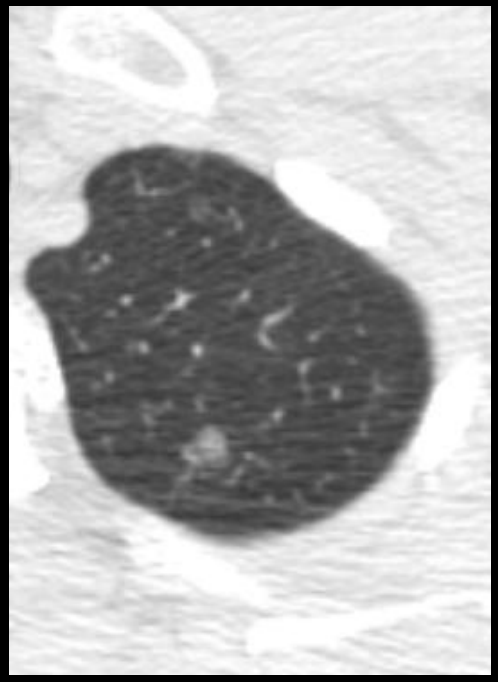


no growth

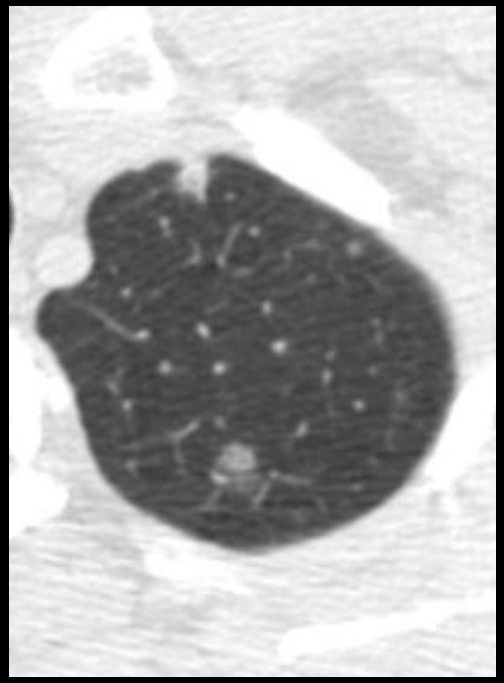
biopsy: malignant cells

surgical resection

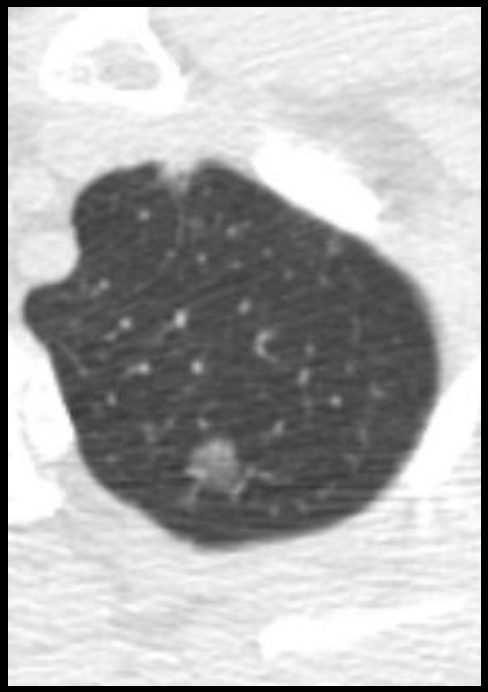
1.1 cm bronchioloalveolar carcinoma, no invasion



July 2007



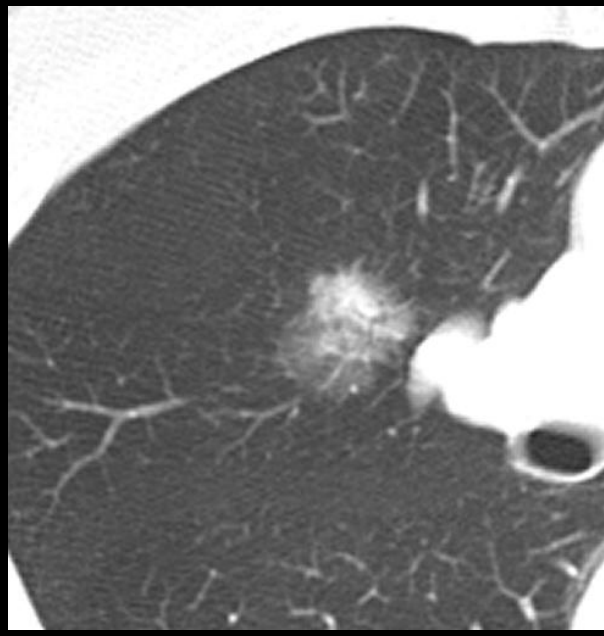
March 2008



July 2008

growth rate > 380 days

Slow growing BAC



2009

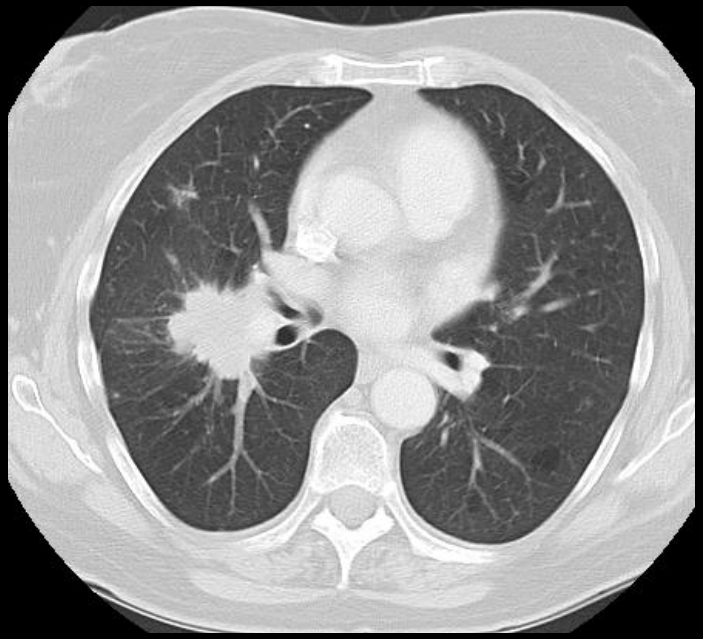
2010

2011

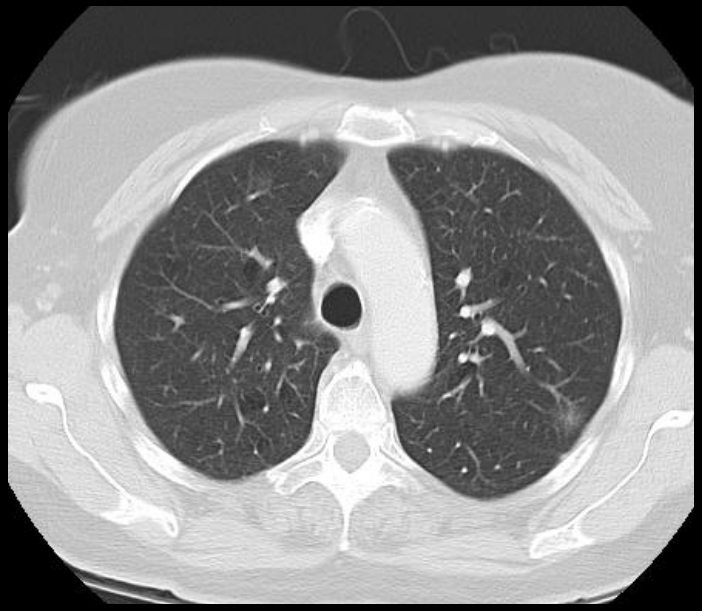
overdiagnosis bias

- indolent disease
- small subgroup
  - non-invasive growth
    - GGO
    - lepidic growth, growth along preexisting alveolar structures
  - slow growing
  - cured with resection
  - often multiple

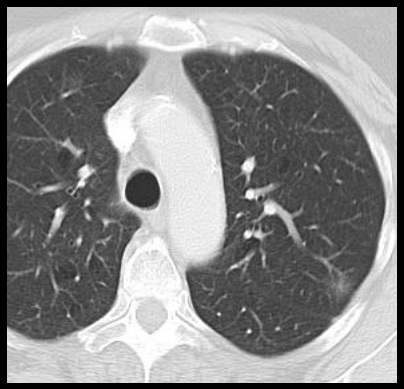
multifocal adeno ca / BAC



2004



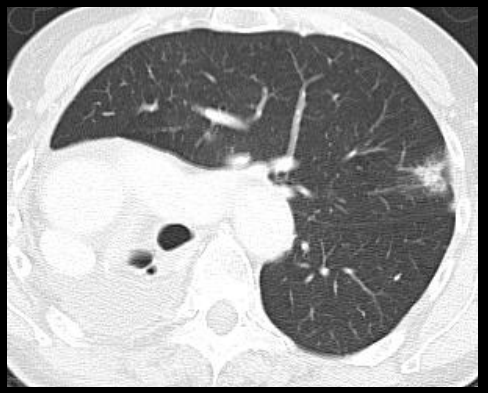
multifocal adeno ca / BAC



2004

2006

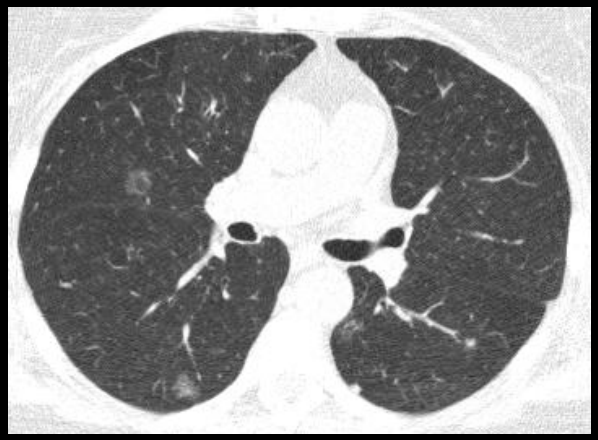
2009

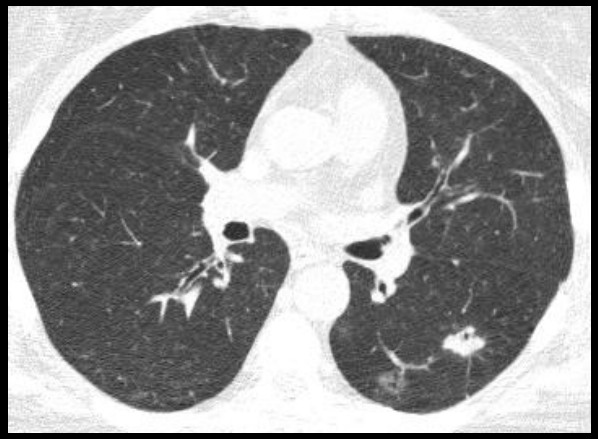


2011

Multifocal BAC

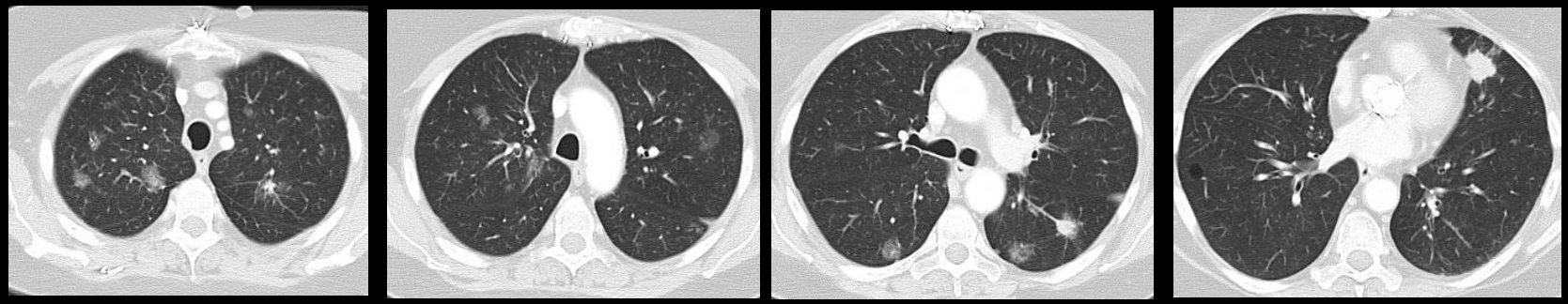
2005



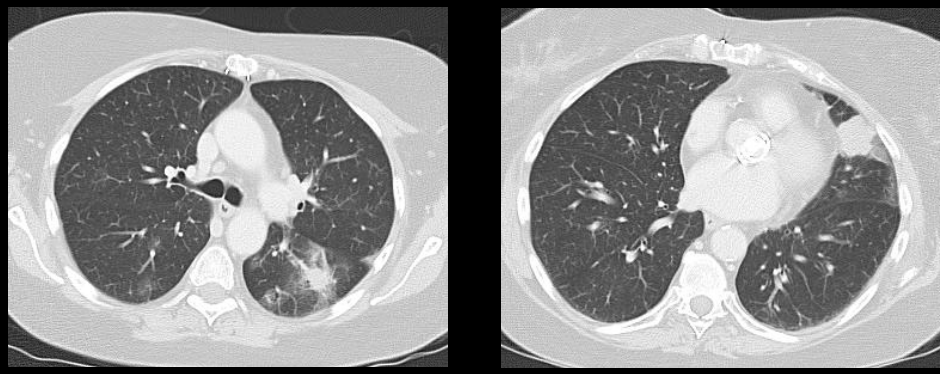


Multifocal BAC

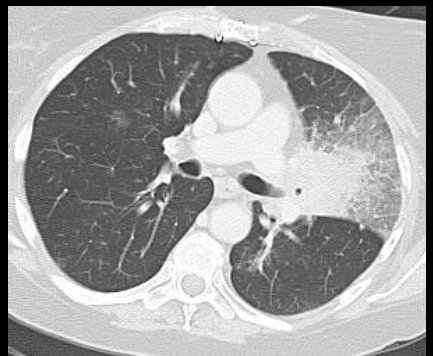
2009



2010



2011



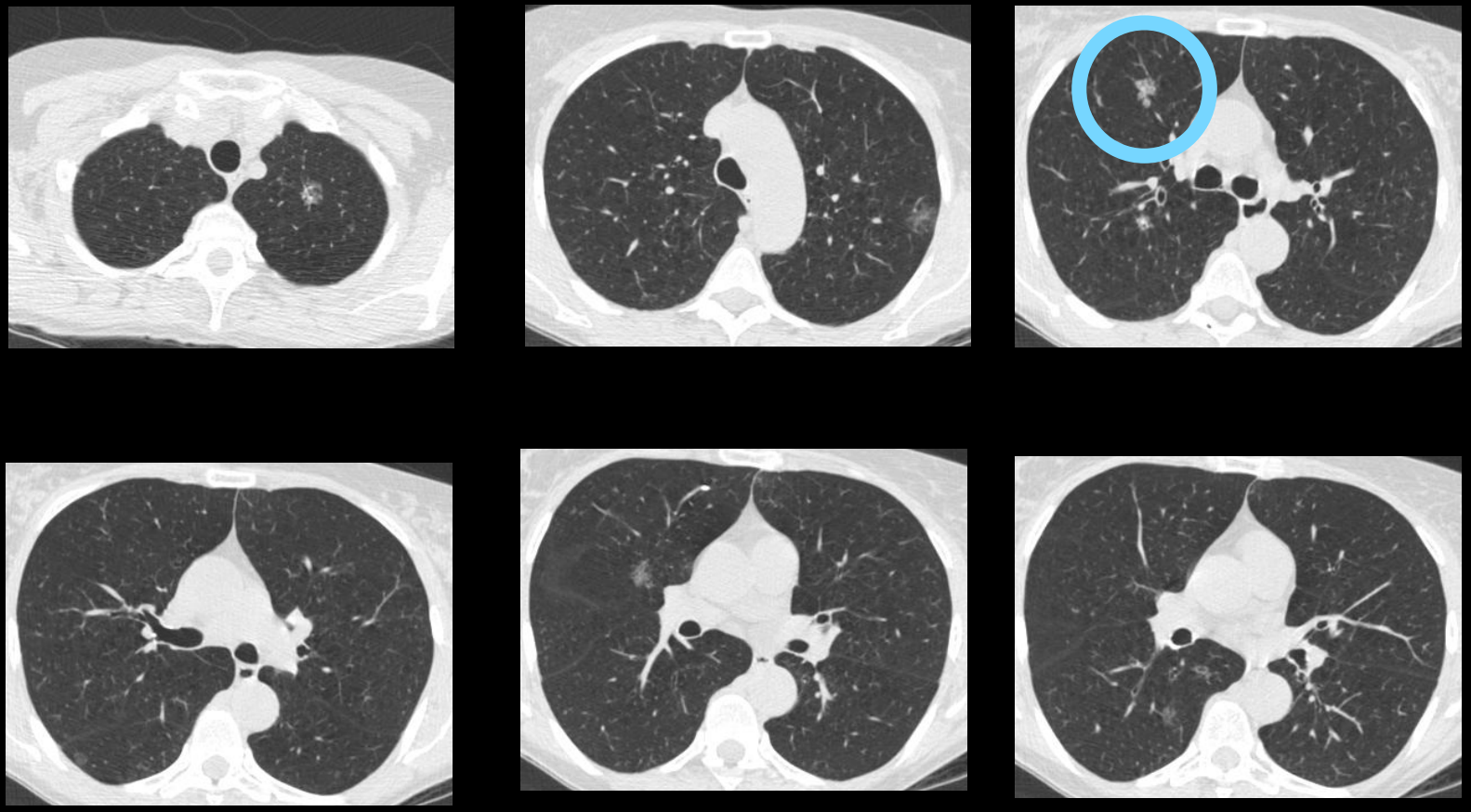
overdiagnosis bias

- indolent disease
- selection
  - imaging (CT, PET)
  - growth analysis
  - biomarker (genetic markers)

?

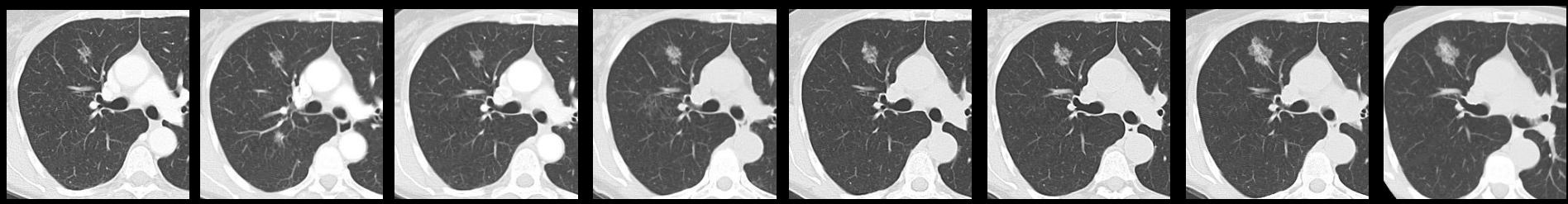
multifocal BAC

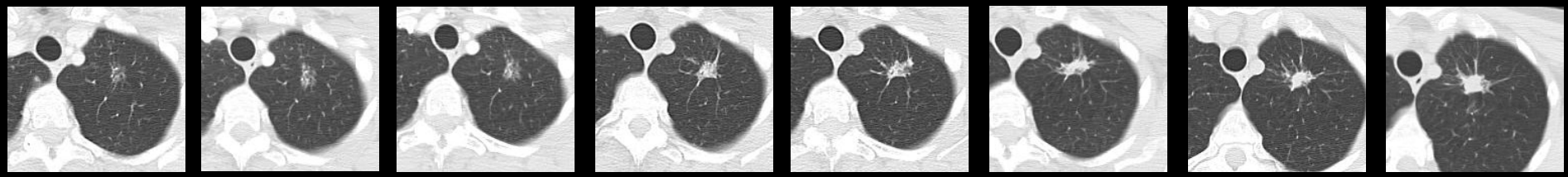
2007



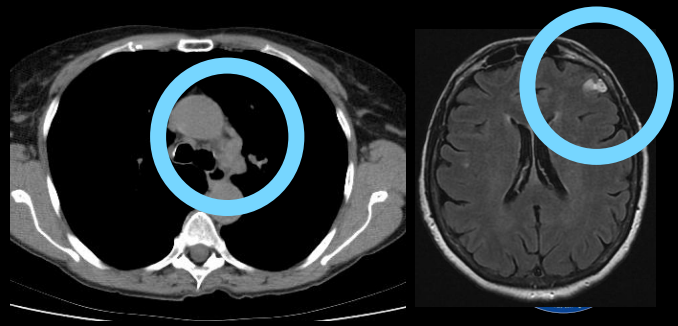
multiple GGOs, most suspicious RUL was biopsied: adeno-ca
no treatment, had semiannual follow up CTs

May 07 Sep 07 Oct 08 Oct 09 Apr 10 Oct 10 May 11 Aug 11





May 11 Aug 11

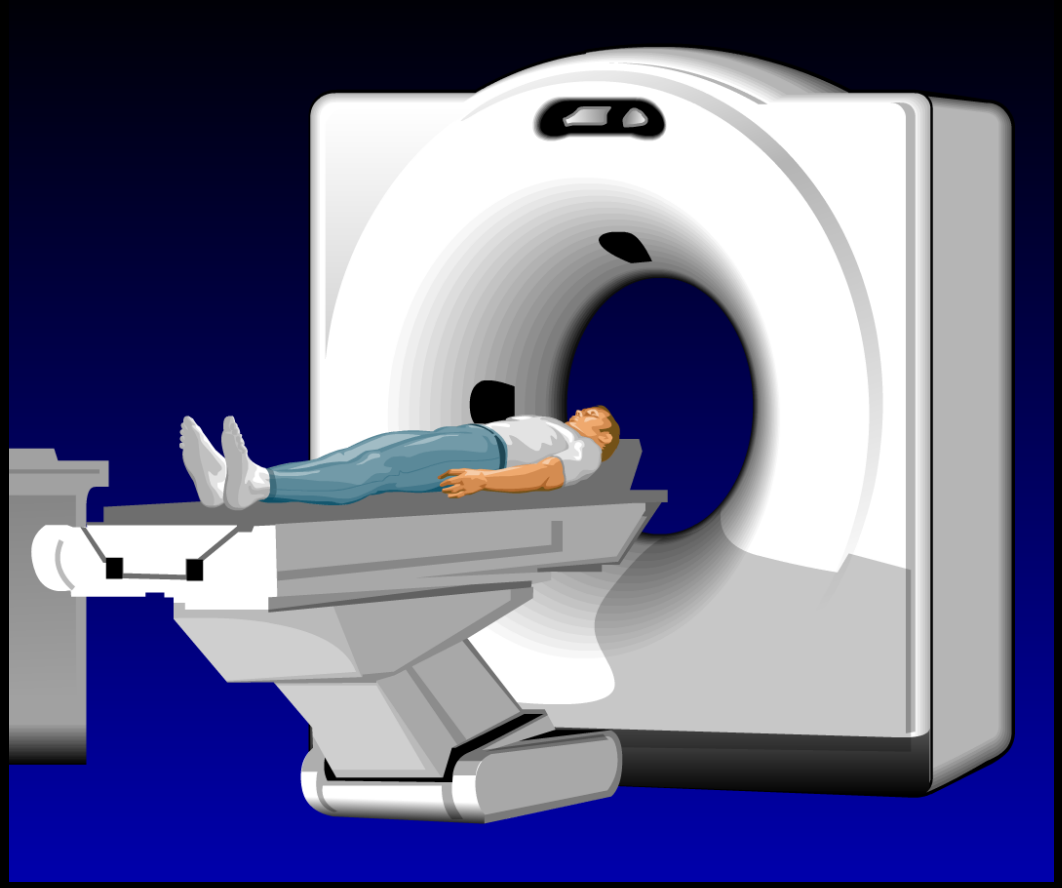


Screening – beyond mortality

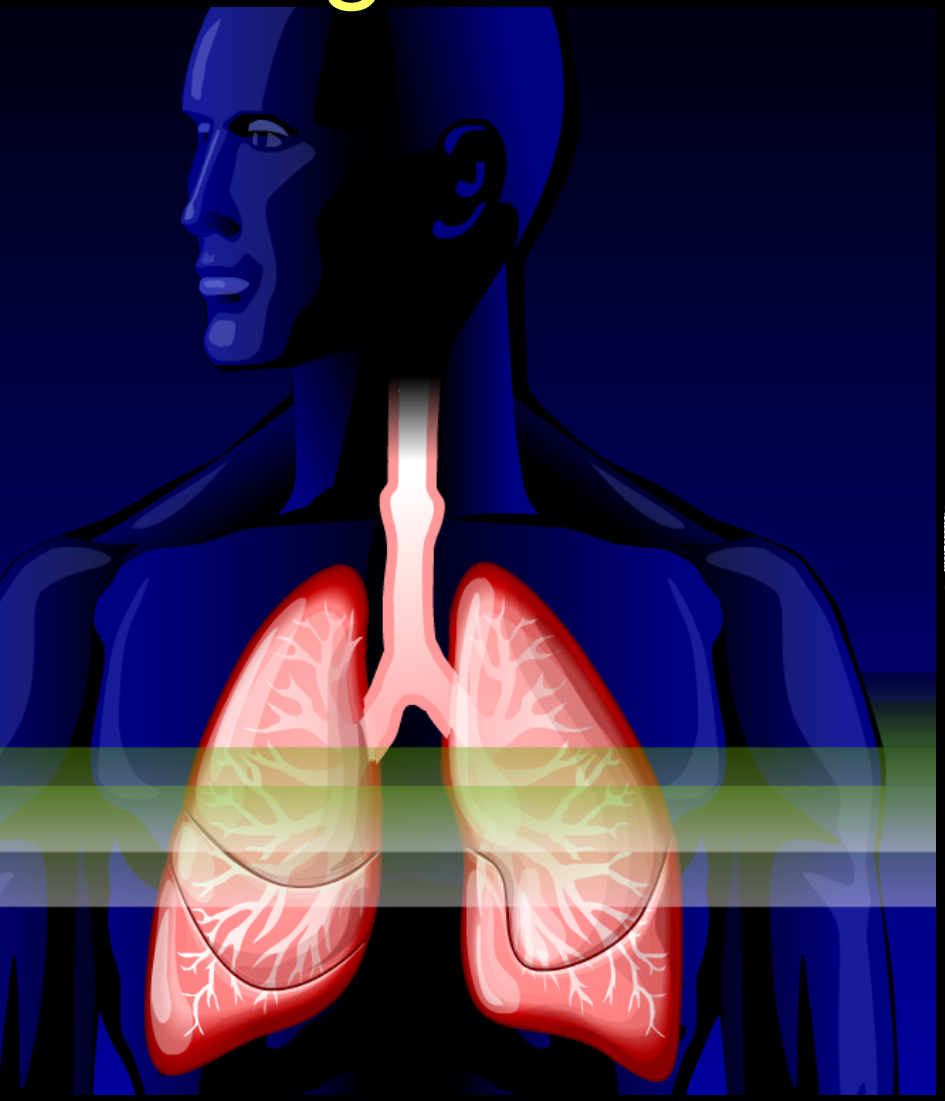
- nodules and false positives
- management of cancers (overdiagnosis)
- radiation exposure
- selection of individuals at risk
- the solution

Lung Cancer Screening – Method

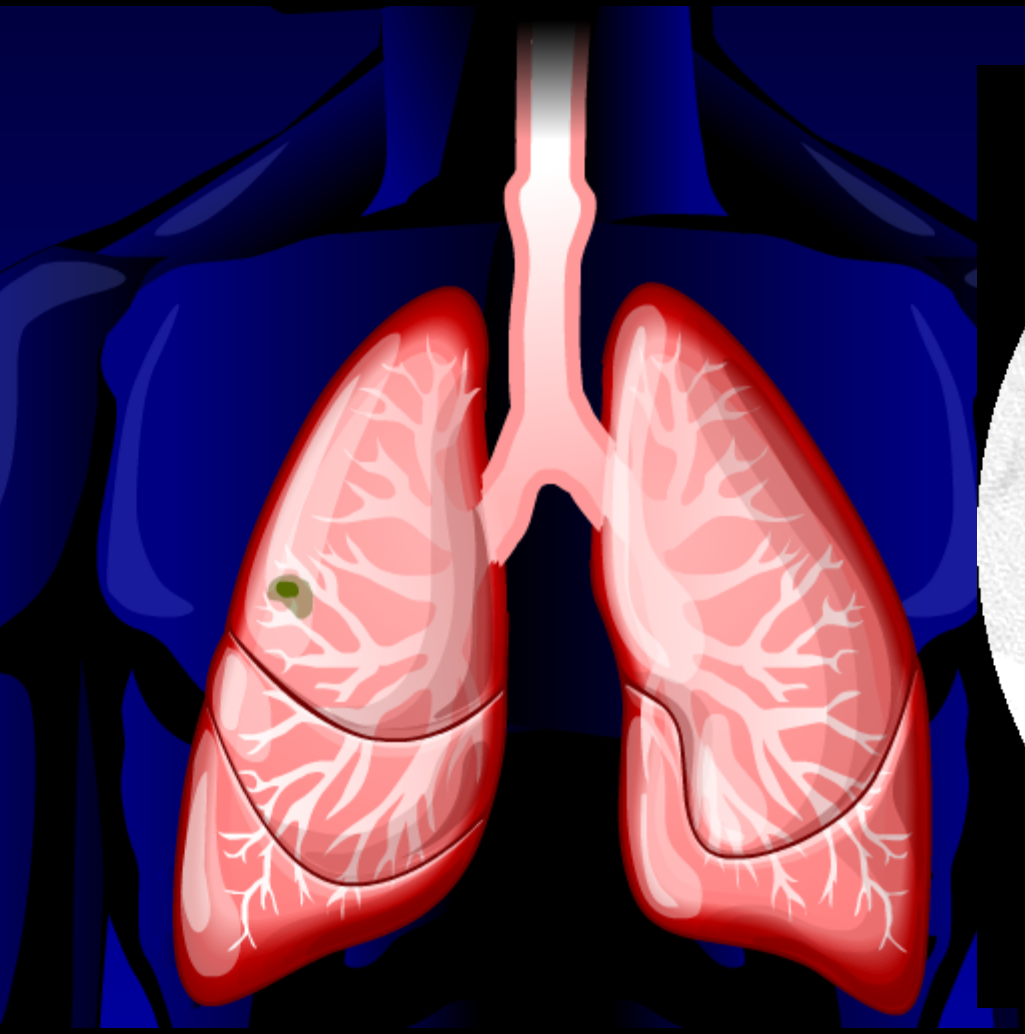
- low-dose
- 40-60 mA
- 120 kV
- 1 mm – 1.25 mm

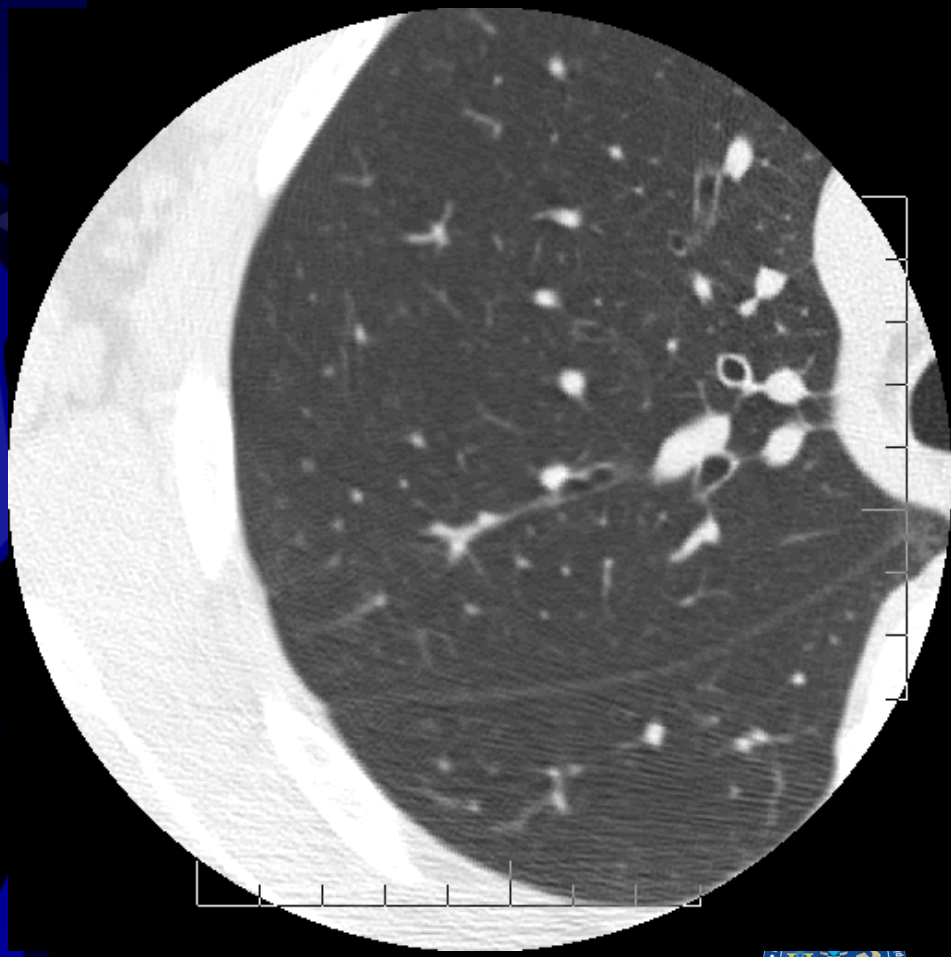


Lung Cancer Screening – Method



Lung Cancer Screening – Method





Lung Cancer Screening

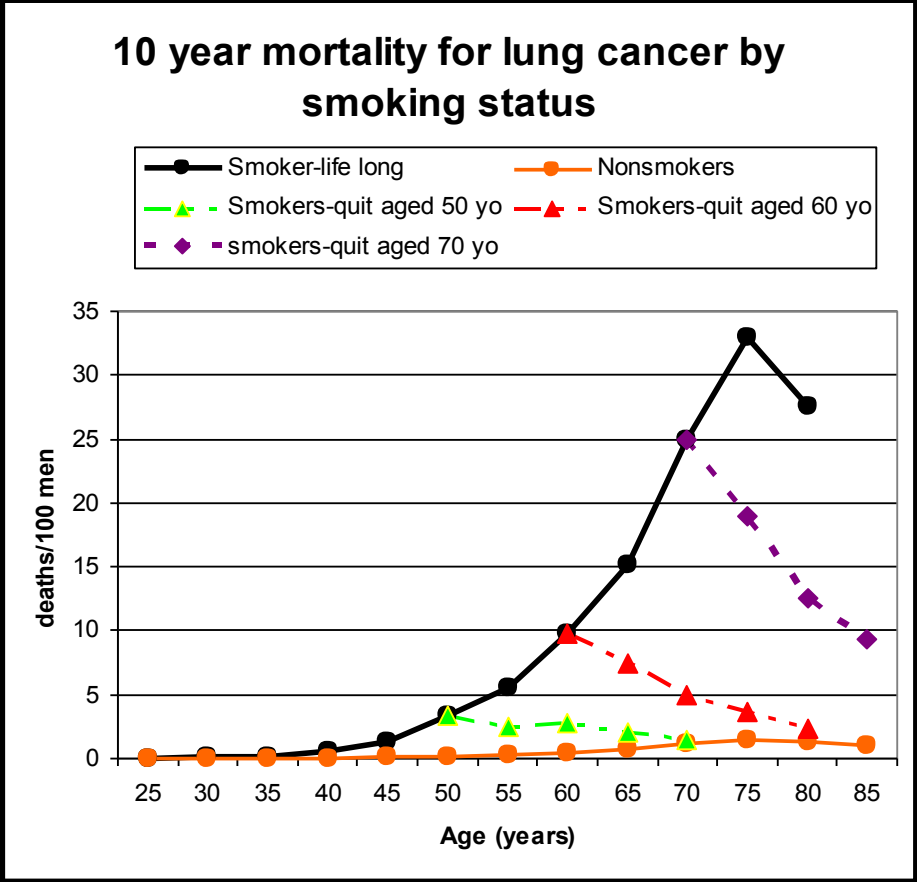
Radiation risk

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**

Screening – how long?

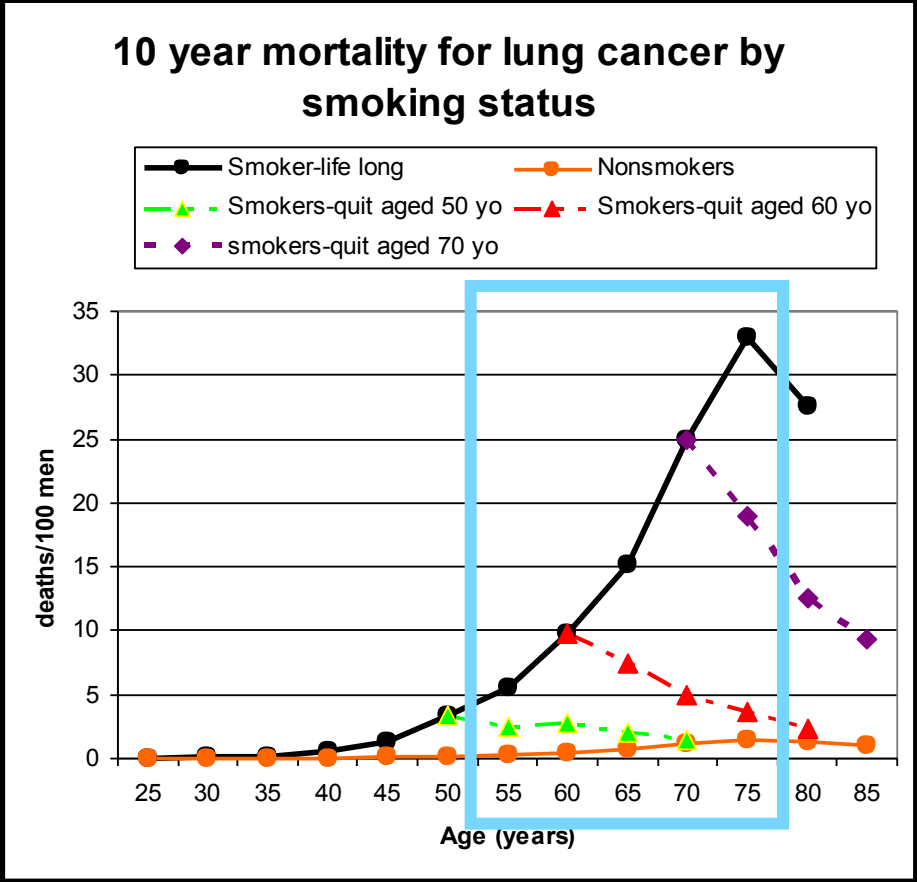
- detectable risk factor or disease marker
  - smoking and ex-smoking population



courtesy
N Young, NZ

Screening – how long?

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

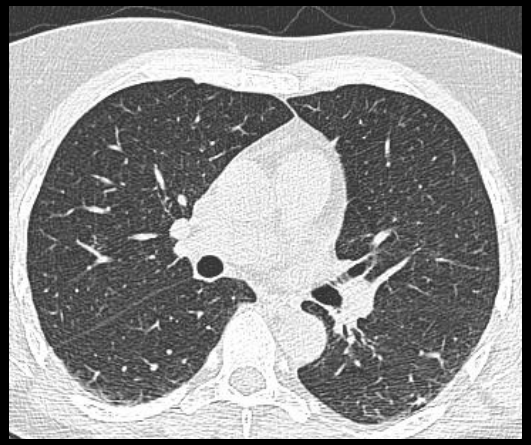


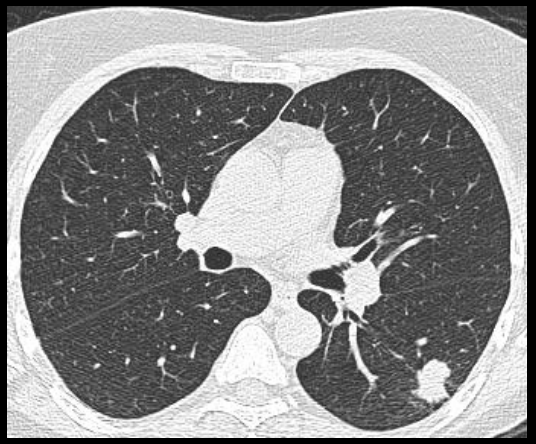
courtesy
N Young, NZ

Screening – how often?

baseline 50 - 55 years

annual / biennial until 75 - 80 years



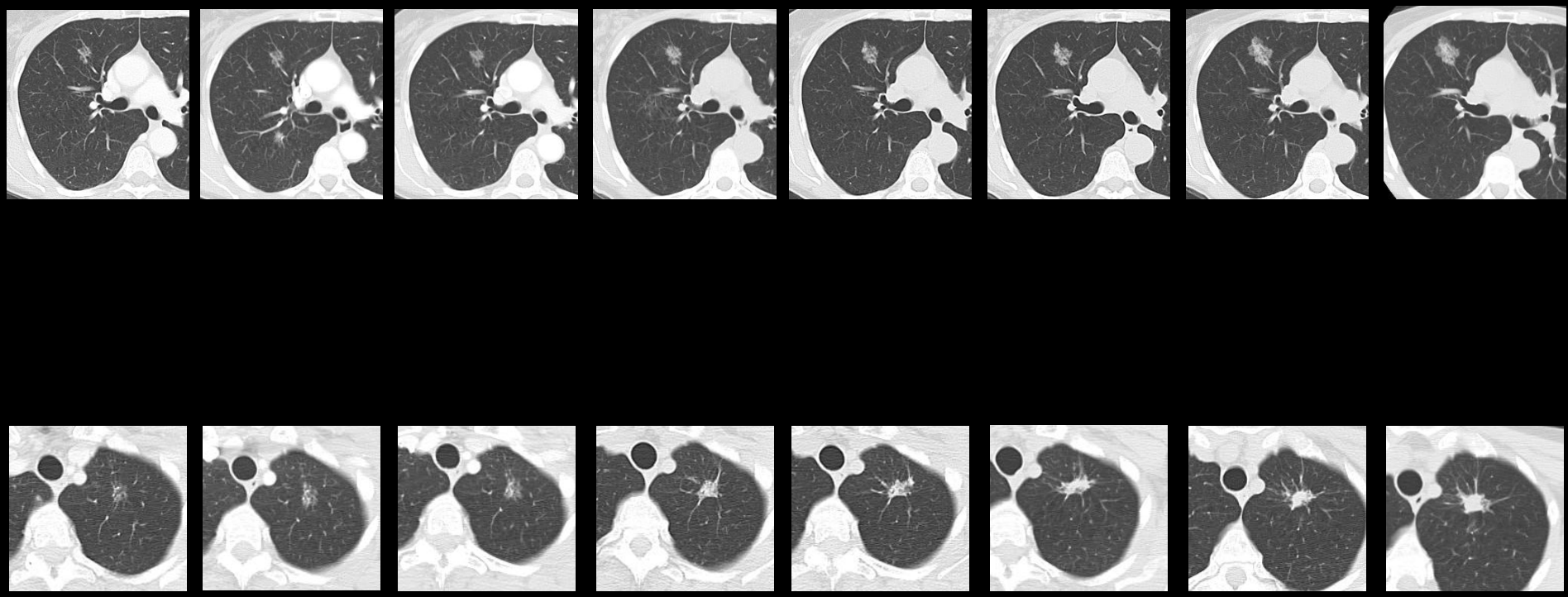


baseline → annual (no show) → 2 years

2006

2007

2010


May 07
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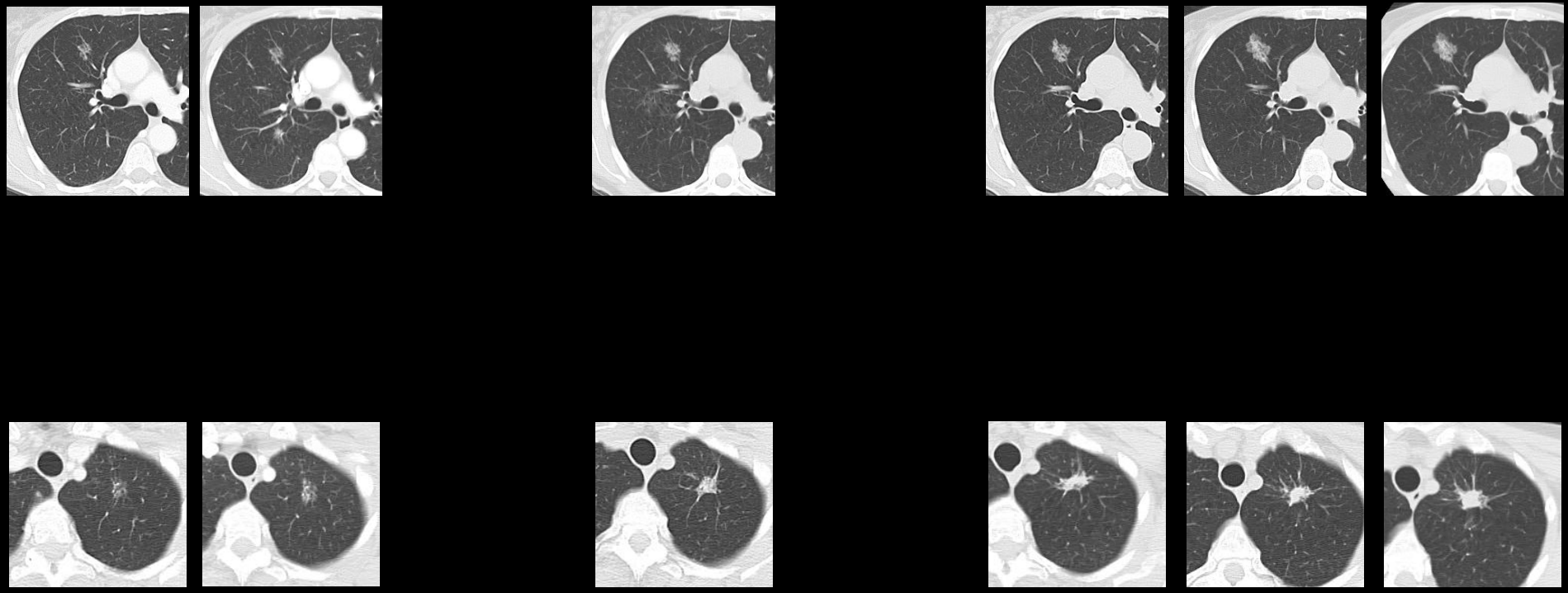
Aug 11

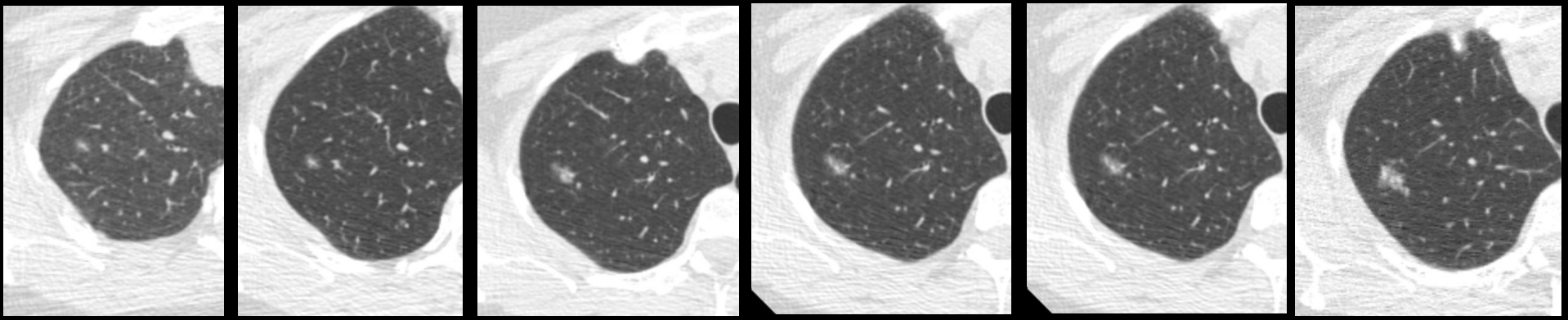
May 07 Sep 07 Oct 09 Oct 10 May 11 Aug 11



Lung Cancer Screening

baseline 50 - 55 years

annual / biennial until 75 - 80 years



2006 2007 2008 2009 2010 2011

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)

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.”

Ontario - demographics

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

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
  Stage 1 (75%)
- *ever* smokers 13,200 lung cancers
  9,900 Stage 1

? $ saved

Lung Cancer Screening – Whom?

- better selection of “at risk” population

individual profile

- multifactorial risk assessment

  smoking, family history, spirometry, BMI, education

  Pan-Canadian Lung Cancer Screening Study

- sputum analysis
- blood analysis (biomarkers)

M Tammemagi & PLCO Study Group

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