ESMO 2012 – CYE session

Screening & early detection of lung cancer

J. Vansteenkiste

Respiratory Oncology Unit
Dept. Pulmonology
Univ. Hospital Leuven
Leuven Lung Cancer Group

Disclosure

J. Vansteenkiste is holder of the Amgen Chair in Supportive Cancer Care at the Leuven University (research funding)

J. Vansteenkiste is holder of the Eli-Lilly Chair in Respiratory Oncology at the Leuven University (research funding)

J. Vansteenkiste is holder of the Astra Zeneca Chair in Personalised Lung Cancer Care at the Leuven University (research funding)

Screening and early detection

- The lung cancer epidemic
- Conditions for successful screening
- Lessons from history
- Low-dose CT screening
  - Non randomised data
  - Randomised controlled trials
  - Issues for implementation
  - Conclusion-Example of recent statement
- Biomarkers
- Endoscopy

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Screening and early detection
> lung cancer epidemic

Cause	Deaths/Year
Hypertension	7.8 M
Smoking	5.0 M
High cholesterol	3.9 M
Malnutrition	3.8 M
Sexual transmission	3.0 M
Poor diet	2.8 M
Overweight	2.5 M
Physical inactivity	2.0 M
Alcohol	1.9 M
Indoor pollution	1.8 M
Poor sanitation	1.6 M

Lopez et al, Lancet 367: 1747–1757, 2006

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Screening and early detection
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Lopez et al, Lancet 367: 1747–1757, 2006 *and* Globocan 2008

	Lung Cancer	
	Estimated numbers	
	Cases	Deaths
World	1,607,000	1,375,000
EU-27	288,000	253,000

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Screening and early detection > prevention

Prevention	Action	Disease	Illness
Primary	**Avoid occurence of disease** ***(population)***	**No**	**No**
Secondary	**Diagnose and treat in early stage to avoid morbidity/mortality** ***(selected population)***	**Yes**	**No**
Tertiary	**Reduce negative impact of existing disease** ***(patient groups)***	**Yes**	**Yes**

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Screening and early detection > principles

- **Aim of screening**
  - Diagnose in an earlier stage (**stage shift**)
  - Treat in earlier stage (**curative therapy**)
  - Avoid mortality (survival not a valid endpoint, must be **reduction of disease-specific mortality**)
- **Conditions**
  1. Sensitive test for detection of smaller lesions — 1 SENSITIVITY
  2. Smaller lesions ~ earlier stage — 2 STAGE
  3. Effective treatment — 3 THERAPY
  4. Acceptable morbidity and cost — 4 FEASIBILITY

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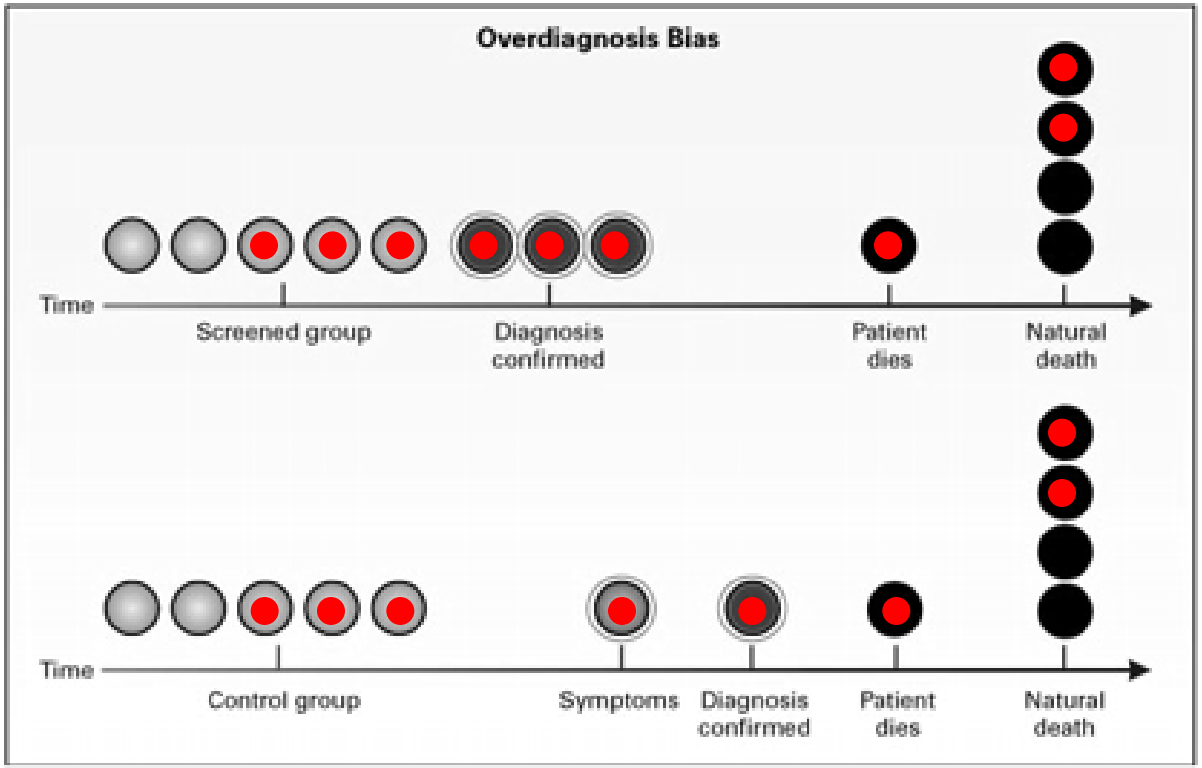
Screening and early detection > overdiagnosis bias



Patz et al, N Engl J Med 34 3:1627-1633, 2000

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Screening and early detection > historical RCTs

- **Historical randomised screening studies**
  - **4 large studies started in 70-ies (>37,000 patients)**
  - **In heavy smokers aged 45+**
  - **Based on**
    - **chest XR ± sputum cytology *vs.* chest XR [1,2,3]**
    - **chest XR and sputum cytology vs. Observation only [4]**
    - **variable test frequency (q4 months, q1 or q3 years)**
- **Negative: no reduction in lung cancer related mortality**

1 Frost et al, Am Rev Respir Dis 130:549-554, 1984
2 Flehinger et al, Am Rev Respir Dis 130:555-560, 1984
3 Fontana et al, Am Rev Respir Dis 130:561-565, 1984
4 Kubic et al, Cancer 57:2427-2437,1986

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Screening and early detection > chest XR in PLCO* trial

* Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer screening trial

- **RCT with 154,901 participants (ages 55-74)**
  - **77,445 annual chest XR for 4 years**
  - **77,456 to usual care**
- **Endpoints:**
  - **Primary: mortality from lung cancer**
  - **Secondary: lung cancer incidence, complications of diagnostic procedures, all-cause mortality**
    - **cumulative lung cancer incidence rates 201 *vs.* 192 per 100,000 person-years (RR 1.05; *NS*)**
    - **stage and histology similar between groups**

Oken et al, JAMA 306: 1865-1873, 2011

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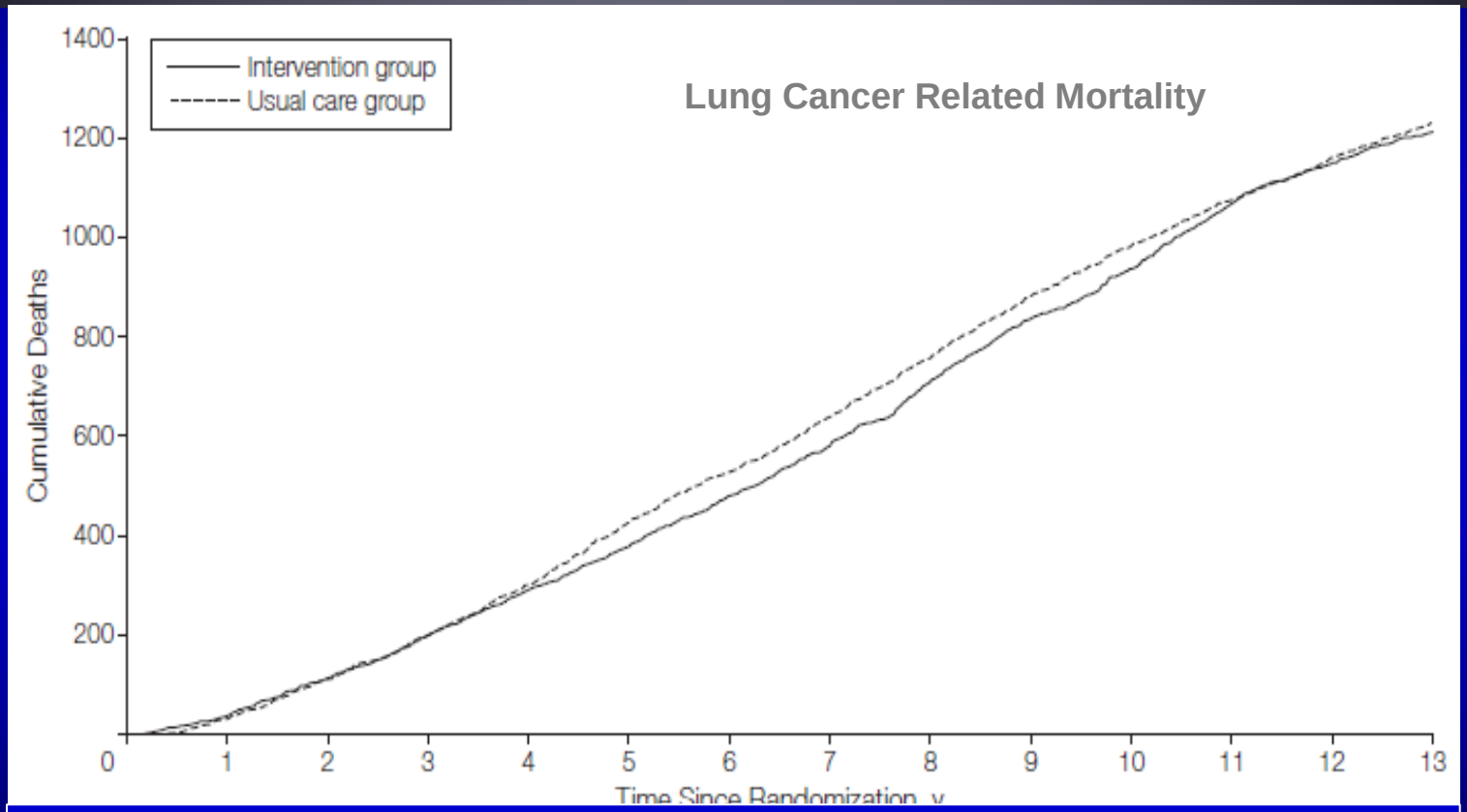
Screening and early detection > chest XR in PLCO trial



1213 (XR) vs. 1230 (OBS) lung cancer deaths (RR 0.99; *NS*)

Oken et al, JAMA 306: 1865-1873, 2011

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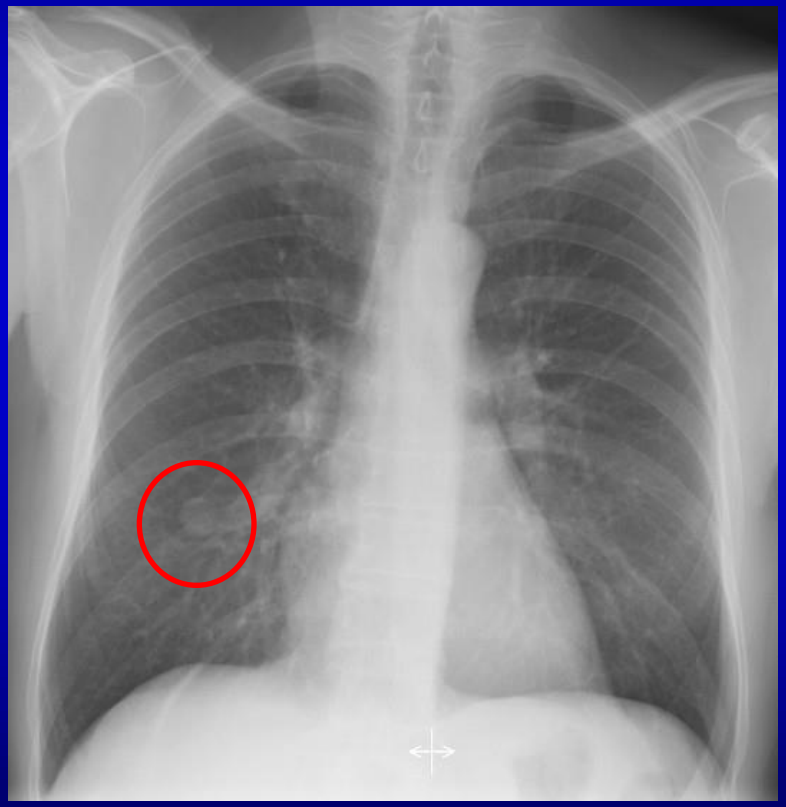
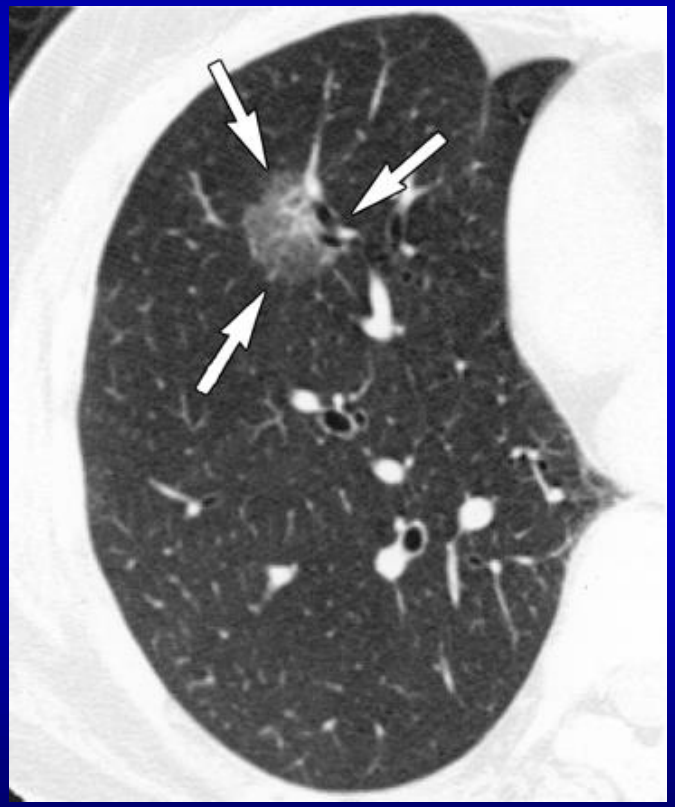
Screening and early detection
> condition 1: sensitive tool





1 SENSITIVITY

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Screening and early detection
> condition 1: sensitive tool

- **Non-randomised LD-CT trials**
  - **Open studies in 1000-1500 in smokers aged 40+**
  - **CT detects smaller lesions (<1.5 cm) missed at XR**
  - **CT detects more cases (prevalence rate e.g. 0.8% *vs.* historical 0.3%)**
  - **Frequent stage I resectable disease**
  - **Better survival**
  - **??? more stage shift (prevalence rate of advanced disease e.g. 0.3% *vs.* 0.2%)**
  - **??? effect on lung cancer mortality**

1 SENSITIVITY

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Screening and early detection
> non randomised LD-CT data e.g. I-ELCAP

- 31,567 asymptomatic persons at risk for lung cancer
  - LD-CT between 1993 through 2005
  - 27,456 repeated screenings (7-18 months)
- Lung cancer in 484 participants
  - 412 (85%) clinical stage I
  - estimated 10-y survival rate 88% (92% in resected cases)
- Conclusion: LD-CT can detect curable lung cancer

I-ELCAP, N Engl J Med 355: 1763-1771, 2006

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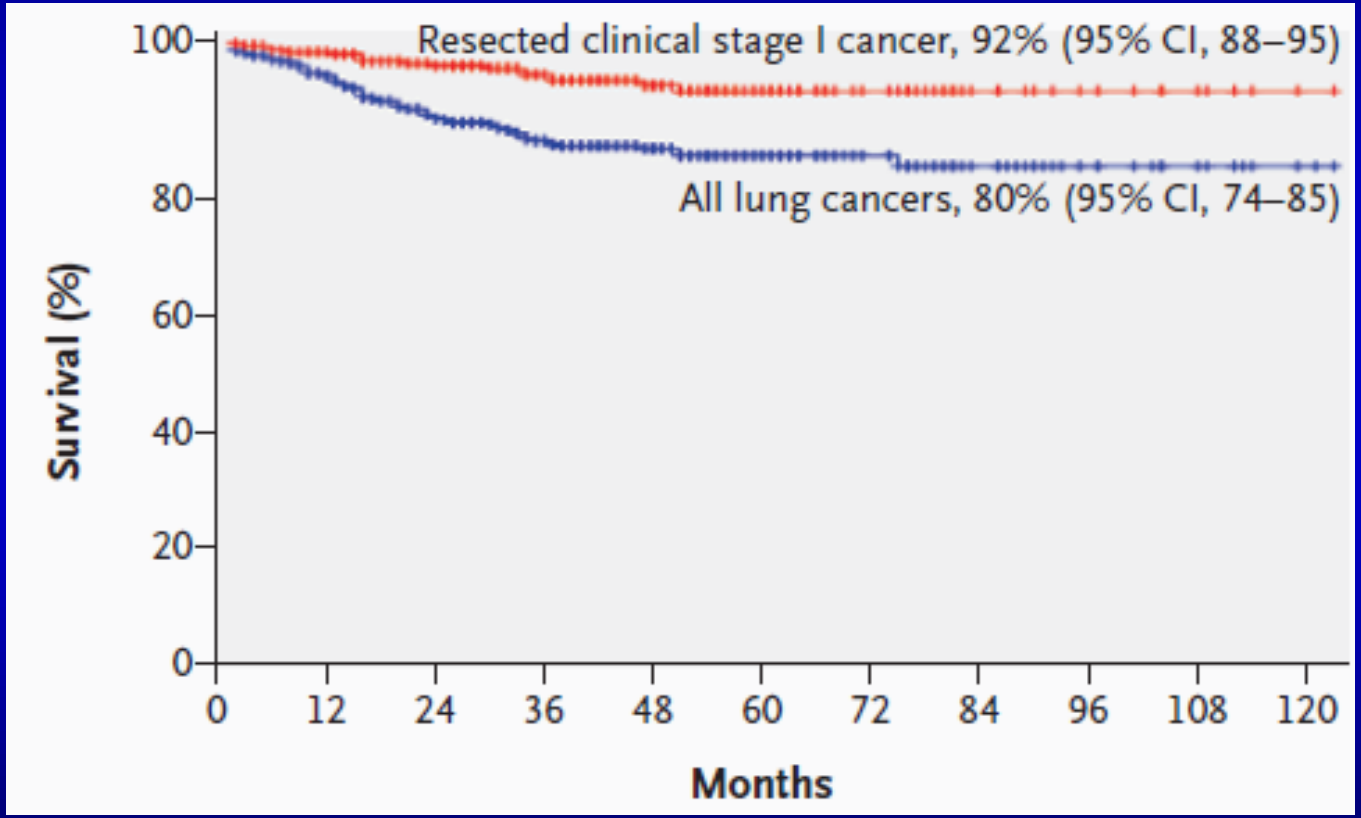
Screening and early detection
> non randomised LD-CT data e.g. I-ELCAP



I-ELCAP, N Engl J Med 355: 1763-1771, 2006

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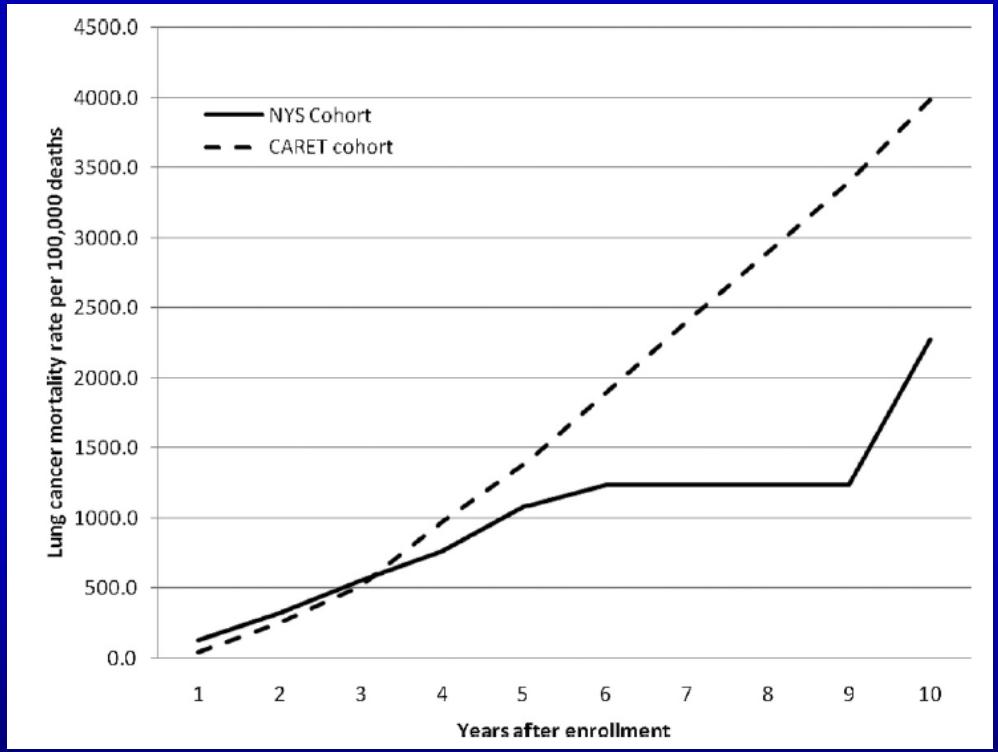
Screening and early detection
> ? reduced lung cancer related mortality

- **Historical comparison**
  - **NY ELCAP (n=7995)**
  - **CARET: prevention study in similar patient group**
  - **correction for possible smoking cessation**
- **SMR calculations**
  - **21/100, 000 *vs.***
  - **57,4/100,000**



Henschke et al, Lung Cancer 71: 328-332, 2011

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Screening and early detection
> NLST

National Cancer Institute press release November 2010

Initial results show mortality benefit with LD-CT screening

Twenty percent fewer lung cancer deaths compared to chest XR screening

hhttp://www.cancer. gov/newscenter/pressrelease/NLSTresultRelease

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Screening and early detection > NLST: design

- **Large RCT based on previous feasibility trial (Lung Screening Study*)**
  - **LDCT versus XR screening**
  - **Primary endpoint: 90% power to detect a 21% decrease in lung cancer mortality**
  - **33 participating centres**
  - **53,454 eligible participants (age 55-74), ≥30 PY smoker or quit within previous 15 years**
  - **3 yearly screening rounds + 3.5 years follow-up**
  - **All screening CT and XR standard protocol, but no standard diagnostic follow-up or diagnostic evaluation**

* Gohagan et al, Lung Cancer 47: 9-15, 2005

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Screening and early detection
> NLST: results

	CT	XR	RR
Positive result	**24.2%**	**6.9%**	
False pos result	**23.3%**	**6.5%**	
Lung cancer	**1060 (645/100,000 PtY)**	**941 (572/100,000 PtY)**	**1.13 [1.03;1.23]**
adeno	***36.3%***	***35.2%***	
stage I	***50%***	***31.1%***	
stage IV	***21.7%***	***36.1%***	
Lung cancer deaths	**346 (247/100,000 PtY)**	**425 309/100,000 PtY)**	**-20% [-6.8;-26.7] *P*=0.004**
All cause deaths	**1877**	**2000**	**-6,7% [-1.2;-13.6] *P*=0.02**

1 SENSITIVITY

2 STAGE

Δ= 79

NSLT team, N Engl J Med 365: 395-409, 2011

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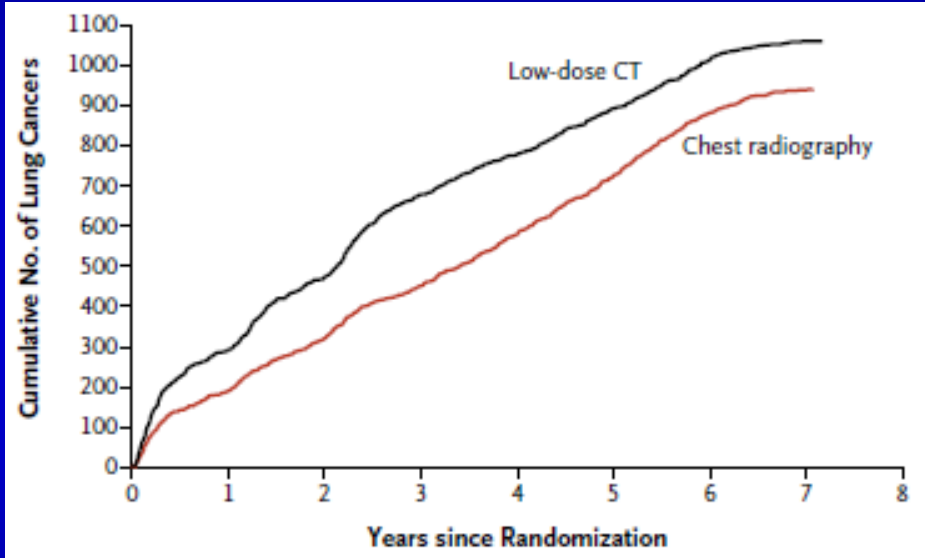
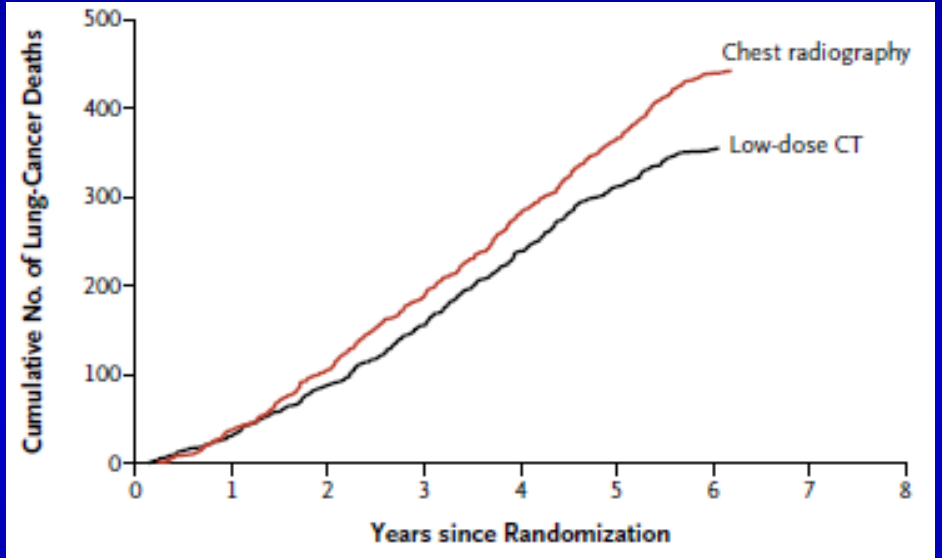
Screening and early detection
> NLST: results



Incidence RR 1.13 [1.03-1.23]



Lung Cancer deaths -20% [-6.8;-26.7]

NSLT team, N Engl J Med 365: 395-409, 2011

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Screening and early detection
> European RCTs

- 6 ongoing trials - enrolled ~32,000 people
- ~ 150,000 person-years of FU
- In addition, UKLS trial feasibility has started (4,000, further plan up to 32,000)
- Largest study (NELSON): final results (mortality data) expected 2015-2016

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Screening and early detection
> European RCTs (recruited)

	NLST	NELSON	DLST	ITALUNG	DANTE
Country	USA	NL/Belgium	Denmark	Italy	Italy
Number of sites	33	4	1	5	3
Number controls	26,732	7,907	2,052	1,593	1,196
Number screened	26,722	7,557	2,052	1,613	1,276
Age range (year)	55-74	50-75	50-70	55-69	60-74
Smoking history	≥30/<15	>15/<10	≥20/<10	≥20/<10	≥20/<10
Control arm	XR	Usual care	Usual care	Usual care	Usual care*
Screening rounds	3	4	5	4	5
Interval (years) [3]	1	1-1-2-2.5	1	1	1
Nodule evaluation	2D	2D, 3D	2D, 3D	2D	2D
Prevalence detection	NR	0.9%	0.8%	1.5%	2.2%
Incidence detection	NR	0.5%	0.67%	0.4%	4.7%
False positives °	96.4%	1.7%	7.9%	NR	NR
Mortality reduction	20%	(2016)	(2016)	NR	NR

* Chest XR at baseline for controls
° false pos in LDCT arm at baseline

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1. Validity
2. Technical aspects
3. Nodule approach
4. Diagn. Workup/therapy
5. Populations at risk
6. Cost

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Screening and early detection
1. validity: e.g. NLST findings

- Excellent internal validity (balanced arms, good protocol adherence, control arm with XR is fine)
- External validity
  - Specially trained radiologists in expert centres
  - Higher than expected young / highly educated / quit-smoking subjects
  - Degree of overdiagnosis at present unknown: at least 10 more years of follow-up needed

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Screening and early detection
1. validity: e.g. NLST findings

	NLST	US census
Male (%)	59.0	58.5
Age		
55-59 (%)	42.8	35.2
60-64 (%)	30.6	29.3
65-69 (%)	17.8	20.8
70-74 (%)	8.8	14.7
Education		
< High School	6.1	21.3
≥ College	31.5	14.4
Current smoker	48.2	57.1
Median pack years	48.0	47.0

Aberle et al, J Natl Cancer Inst 102: 1771-1779, 2010

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Screening and early detection
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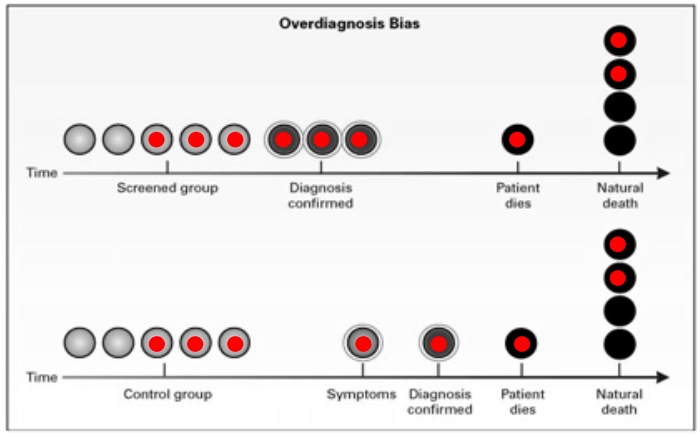

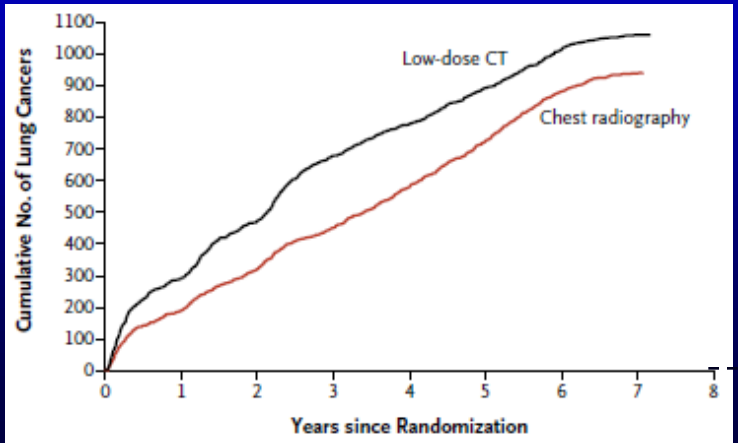

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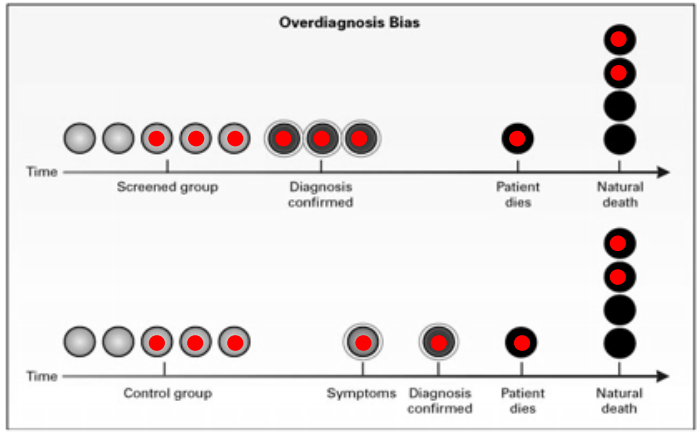

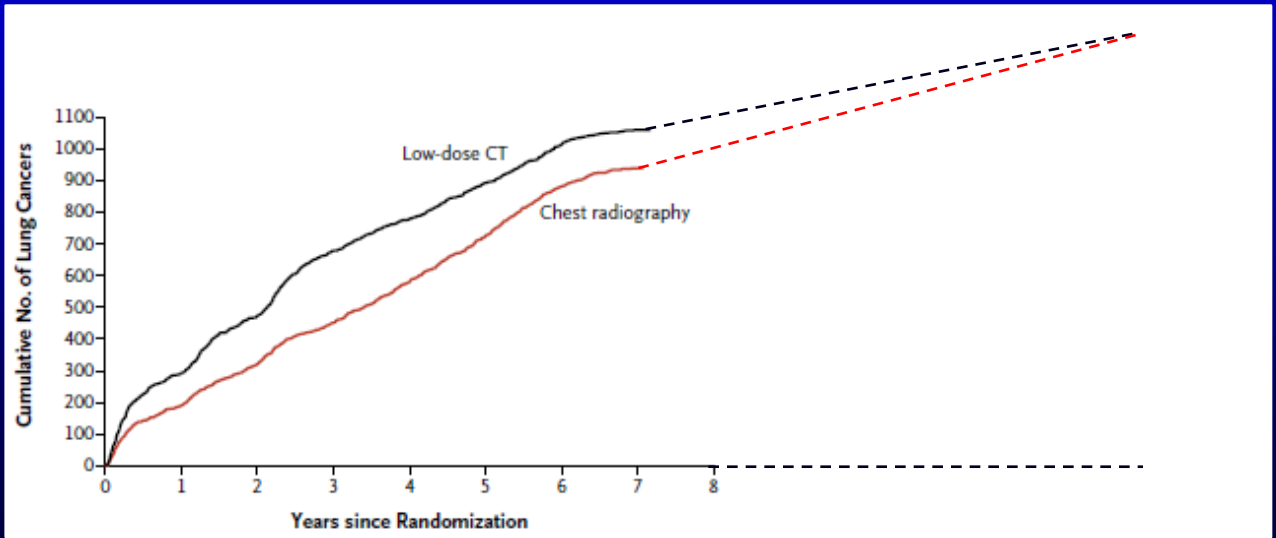

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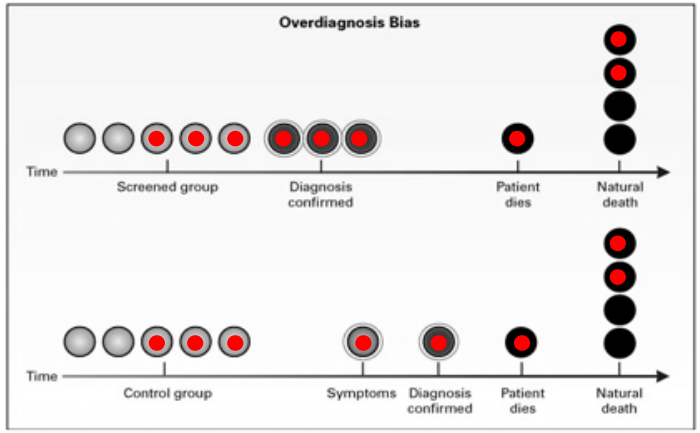

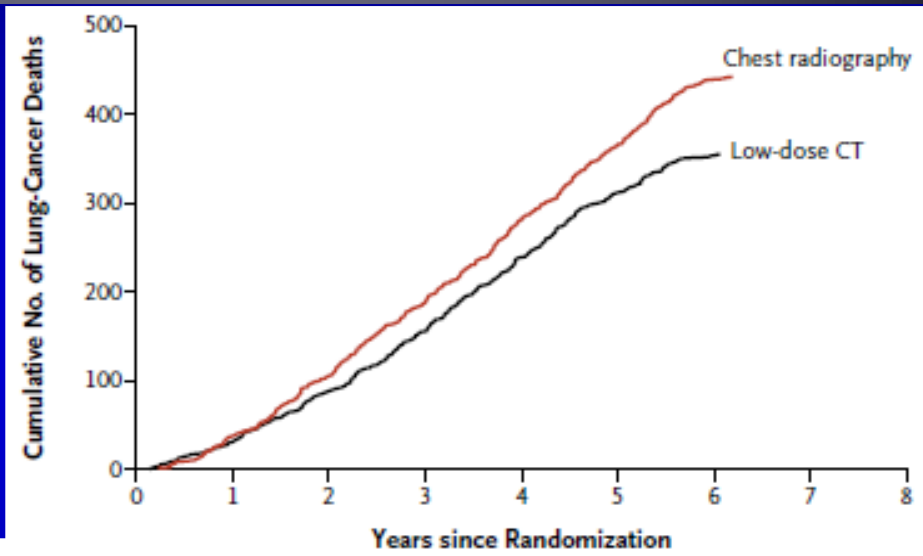

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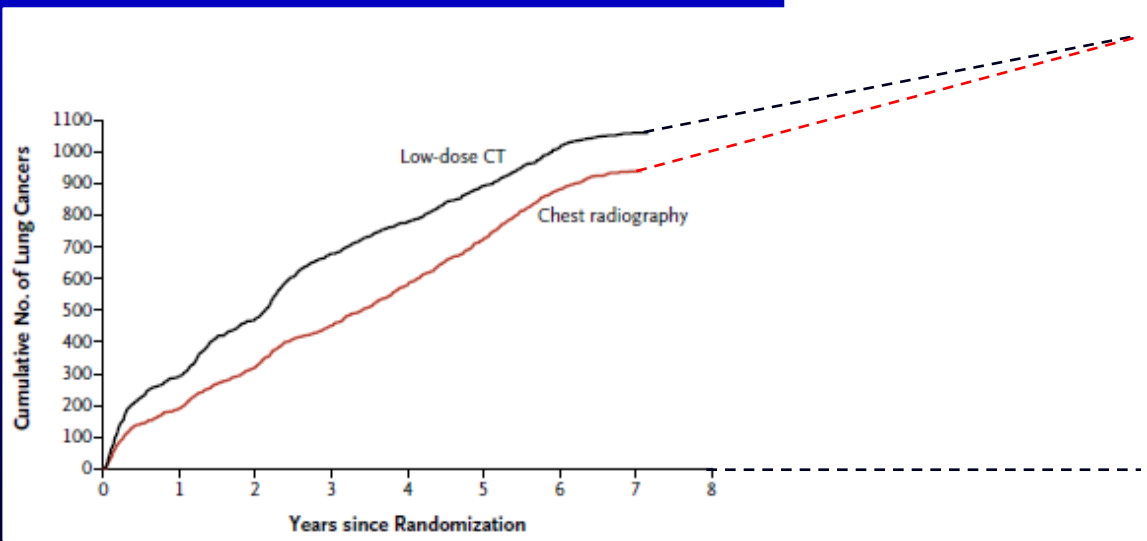

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Screening and early detection
1. validity: Mayo Clinic non-RCT modeling

TRIAL: open LD-CT trial with 5 annual screenings in 1520 patients
MODELING: *P*<0.05 if for 8000 patients with 6-year follow-up

Model-predicted Outcome according to Follow-up		Control Arm	Screening Arm
Patients diagnosed with lung cancer			
1.5 y follow-up		9.2	22.0*
6-y follow-up	+37%	37.9	51.9†
10-y follow-up		64.6	74.1
15-y follow-up	+9%	97.0	105.5
Lifetime of cohort		171.4	179.0
Lung cancer deaths			
1.5-y follow-up		4.2	4.0
6-y follow-up	-28%	26.5	19.1
10-y follow-up		47.8	36.6
15-y follow-up	-15%	73.5	62.3
Lifetime of cohort	-8%	131.3	120.8
All deaths			
1.5-y follow-up		34.7	34.9
6-y follow-up	-4%	162.8	157.0
10-y follow-up		302.3	293.6
15-y follow-up	-2%	510.7	501.0
Iatrogenic deaths, 6-y follow-up		0.3	0.5

McMahon et al, Radiology 248:278-287, 2008

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Screening and early detection
2. techniques

- **Harmonization of protocols**
  - **Radiological settings (rows in detector, slice thickness, image reconstruction, computer-aid, ...)**
  - **Optimal number of rounds / intervals**

	NLST	NELSON	DLST	ITALUNG	DANTE
Control arm	XR	Usual care	Usual care	Usual care	Usual care*
Screening rounds	3	4	5	4	5
Interval (years) [3]	1	1-2-2.5	1	1	1
Nodule evaluation	2D	2D, 3D	2D, 3D	2D	2D

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Screening and early detection
2. techniques

- **Optimal number of rounds**
  - **NSLT observation**

	Round 1	Round 2	Round 3	3Y follow-up
Lung cancer detection	270 (3.8%)	168 (2.4%)	211 (5.2%)	similar

  - **EU RCT: prevalence detection > incidence detection**
  - **UKLS: explore one single screen**

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Screening and early detection
3. nodule approach

- False positive screening findings may lead to a large number of additional non-invasive and invasive tests
- Efforts to reduce FP rate – use of volumetric analysis
  - Historical studies: high number of indeterminate nodules: from 23% to 51% of patients
- NLST

	CT	XR
Positive result	18,146 (24.2%)	5043 (6.9%)
False pos result	17,497 (96.4%)	4,764 (94.5%)
Lung cancer	649 (3.2%)	279 (5.5%)

- EU: Nelson nodule management

Henschke et al, Lancet 354:99-105, 1999
Mayo Lung Cancer Screening Project

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Screening and early detection
3. nodule approach NELSON

Table 1 NELSON classification of the different non-calcified nodules according to size at baseline screening

Use of 3D (*or* 2D)

NODCAT baseline	Definition
I	Benign nodule (fat/benign calcifications) or other benign characteristics
II	Any nodule, smaller than NODCAT III and no characteristics of NODCAT I
III	Solid: 50–500 mm^3 Solid, pleural based: 5–10 mm d_{min} Partial solid, non-solid component: ≥8 mm d_{mean} Partial solid, solid component: 50–500 mm^3 Non-solid: ≥8 mm d_{mean}
IV	Solid: >500 mm^3 Solid, pleural based: >10 mm d_{min} Partial solid, solid component: >500 mm^3

NELSON
Nederlands-Leuvens Longkanker Screenings Onderzoek

Xu et al, Lung Cancer 54: 177-184, 2006

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IV	Solid: >500 mm^3 Solid, pleural based: >10 mm d_{min} Partial solid, solid component: >500 mm^3

Use of 3D (*or* 2D)

Continue as planned with next LDCT round

Indeterminate test: repeat scan 3-4 mo

Refer for diagnostic work-up

Xu et al, Lung Cancer 54: 177-184, 2006

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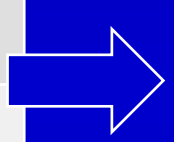
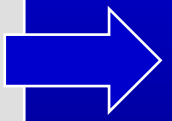
Screening and early detection
3. nodule approach NELSON

VDT	GROWCAT
>600 days	A
400-600 days	B
<400 days	C



Continue as planned with next LDCT round



Refer for diagnostic work-up

Xu et al, Lung Cancer 54: 177-184, 2006

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Screening and early detection
3. nodule approach NELSON

Table 3 NELSON follow-up protocol for non-calcified nodules at annual repeat screening

	Year 1	Year 2	Year 3
Volume	V_1	V_2	V_3
Percentage volume change: PVC (%) (solid nodules only)		$100 \times (V_2 - V_1)/V_2$	$100 \times (V_3 - V_1)/V_1$
Growth		PVC < 25%: no; PVC ≥ 25%: yes	PVC < 25%: no; PVC ≥ 25%: yes
Select lowest VDT (either VDT_v or VDT_d)			
VDT > 600 days: GROWCAT A		Annual CT year 4	Annual CT year 4
VDT 400–600 days: GROWCAT B		Annual CT year 3	Annual CT year 4
VDT < 400 days or new solid component in non-solid lesion: GROWCAT C		Refer to pulmonologist	Refer to pulmonologist

Xu et al, Lung Cancer 54: 177-184, 2006

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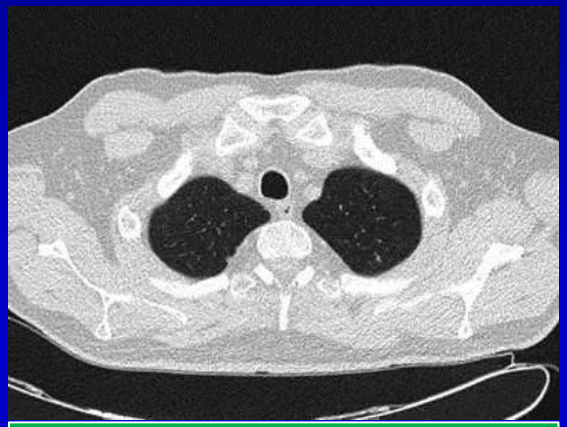
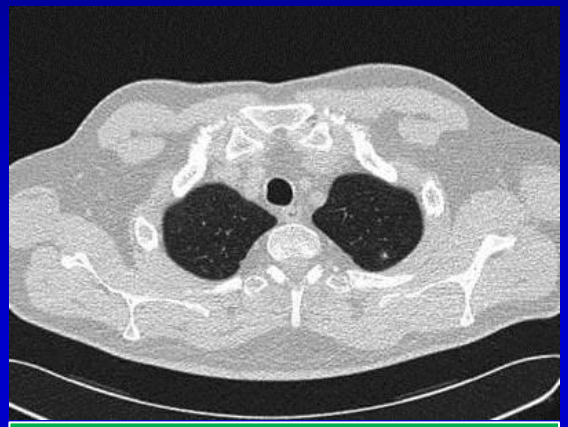
3. nodule approach NELSON



Round 1
NODCAT 2



Round 2
NODCAT 2
% vol change <25%

Round 3
NODCAT 2
% vol change >25%
GROWCAT C

Left superior lobectomy: pT1aN0 adenocarcinoma

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Screening and early detection
3. nodule approach NELSON

- In 1st and 2nd round of screening, 2.6% and 1.8% of the participants had a positive test result
- In 1st round one, sensitivity was 94.6%, NPV 99.9%
- In case of negative 1st round, chances of finding lung cancer
  - 1/1000 after 1 year
  - 3/1000 after 2 years

Van Klaveren et al, N Engl J Med 361: 2221-2229, 2009

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Screening and early detection
5. population at risk

- Using the NLST criteria
  - 7 million persons in the US would be screened
- There are 94 million current/former smokers
- Implementation ...

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Screening and early detection
> UKLS: feasibility phase

- Selection of subjects with high risk for lung cancer
  - according to validated Liverpool Lung Project risk model
- One single round of LDCT screening
  - estimated lung cancer detection rate of about 1.5%
- Nodule categorisation and follow-up according to the NELSON nodule management

Baldwin et al, Thorax 66: 308-13, 2011

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Screening and early detection
5. population at risk

Risk factor/category	Odds ratio[b]	(95% CI)	*P*-value
Smoking duration			<0.001
Never	1.00	Reference	
1–20 years	2.16	(1.21–3.85)	
21–40 years	4.27	(2.62–6.94)	
41–60 years	12.27	(7.41–20.30)	
>60 years	15.25	(5.71–40.65)	
Prior diagnosis of pneumonia			0.002
No	1.00	Reference	
Yes	1.83	(1.26–2.64)	
Occupational exposure to asbestos			
No	1.00	Reference	<0.001
Yes	1.89	(1.35–2.62)	
Prior diagnosis of malignant tumour			0.005
No	1.00	Reference	
Yes	1.96	(1.22–3.14)	
Family history of lung cancer			0.01
No	1.00	Reference	
Early-onset (<60 years)	2.02	(1.18–3.45)	
Late-onset (≥60 years)	1.18	(0.79–1.76)	

Cassidy et al, Br J Cancer 98: 270-276, 2008

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Screening and early detection
6. cost

- **NSLT**
  - **'number needed to screen' to prevent 1 lung cancer death**
  - **'NNS': estimated as the reciprocal of reduction in absolute risk of death from lung cancer in one group vs. the other**
  - **'NNS' result was 320 !**
- **North-American modelling study**
  - **Incremental cost-effectiveness ratio varying between $110,000/QALY and $280,000/QALY**
  - **LDCT screening along *with successful smoking cessation* in *very selected groups* of patients, this could be more cost-effective ($73,000/QALY) than screening alone**

Aberle et al, J Natl Cancer Inst 102: 1771-1779, 2010
McMahon et al, J Thorac Oncol 6: 1841-1848, 2011

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Screening and early detection

- The lung cancer epidemic
- Conditions for successful screening
- Lessons from history
- Low-dose CT screening
  - Non randomised data
  - Randomised controlled trials
  - Issues for implementation
  - Conclusion-Example of recent statement
- Biomarkers
- Endoscopy

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Screening and early detection > conclusions

- LDCT first test with significant reduction in lung cancer mortality through early detection
- Issues to be addressed before implementation of LDCT
  - Target population
  - CT number of rounds and frequency
  - Optimal nodule management
  - Cost-effectiveness compared to anti-smoking actions
- 32,000 patients in 6 European RCTs
  - Final mortality data expected 2015-2016
  - Unique information on screening *vs.* no-screening
  - Additional data from UKLS

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Screening and early detection
> IASLC 2011 statement 1

- **Context and NSLT data**
  - **LDCT first test with significant reduction in lung cancer mortality through early detection**
- **Number of opportunities to improve further this approach**
  - **Ongoing trials. Largest is Dutch-Belgian NELSON, a *population-based* trial of 20,000 smokers, which uses *refined CT* techniques, and will have *cost effectiveness* and *clinical management* data**
  - **IASLC encourages people to be enrolled into screening trials so that further information can be acquired as soon as possible**
  - **Further research needed: evolution in CT technique/protocol, surgical management, definition of risk groups with highest benefit**

http://www.iaslc.org/policies/statement-on-ct-screening/

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Screening and early detection
> IASLC 2011 statement 2

- **Implementation?**
  - **Crucial = multidisciplinary groups of trained specialists in all aspects of early lung cancer**
  - **Appropriate for heavy smokers ages 55-74 to discuss lung cancer screening information with their physicians to assist them in deciding whether to undergo spiral CT screening**
  - **In each country, lung cancer screening benefit, implementation costs and potential harms must be defined in a cultural context, so that national policies about implementation and quality control can be decided. Different nations will need to undertake individual health technology assessments.**
- **IASLC continues to advocate for effective tobacco control, and integrated public health messages for both tobacco control and lung cancer early detection**

http://www.iaslc.org/policies/statement-on-ct-screening/

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Screening and early detection > biomarkers

- **Ideal early detection biomarker**
  - **permits large-scale screening**
  - **applicable on easily accessible specimens through non-invasive procedures**
  - **easy and reproducible quantification**
  - **high sensitivity and specificity**
  - **low cost**

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Screening and early detection > biomarkers

- Stratify high-risk populations for screening studies
  - early detection biomarker in e.g. blood sample
  - improve definition of populations at risk
  - thereby making LDCT screening cost-effective
- Help in the DD of screen-detected nodules

	CT	XR
Positive result	18,146 (24.2%)	5043 (6.9%)
False pos result	17,497 (96.4%)	4,764 (94.5%)
Lung cancer	649 (3.2%)	279 (5.5%)

- Help to define which nodules are the indolent ones

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Screening and early detection > biomarkers

Very large number of early detection biomarker studies

- **Targets**
  - **DNA, promoter hypermethylation, microsatellite instability, loss of heterozygosity (LOH), chromosomal aneusomy**
  - **messenger RNA (mRNA), micro RNA (miRNA)**
  - **tumour-associated antibodies, antigens, proteomic profiles**
  - **volatile organic compounds**
- **Specimens**
  - **bronchial biopsies or lavage**
  - **induced sputum**
  - **buccal/nasal swabs**
  - **plasma, serum, circulating tumour cells**
  - **exhaled breath**

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Screening and early detection > biomarkers

- Many with high sensitivity and specificity (up to 100%) in feasibility studies
- None recommended as tests for screening
  - lack of validation
  - unsure if appropriate for risk individuals or very early stages
- Best candidates
  - miRNAs
    - high tissue specificity and incredible stability -> easily detectable and quantifiable in body fluids
    - promising in work-up of LDCT detected nodules
  - VOCs in exhaled breath
    - non-invasive and repeatable
    - moderate accuracy to distinguish lung cancer from controls

Boeri et al, Proc Natl Acad Sci 108: 3713-3718, 2011
Shen et al, BMC Cancer 11: 374, 2011
Dragonieri et al, Lung Cancer 64: 166-170, 2009

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Screening and early detection

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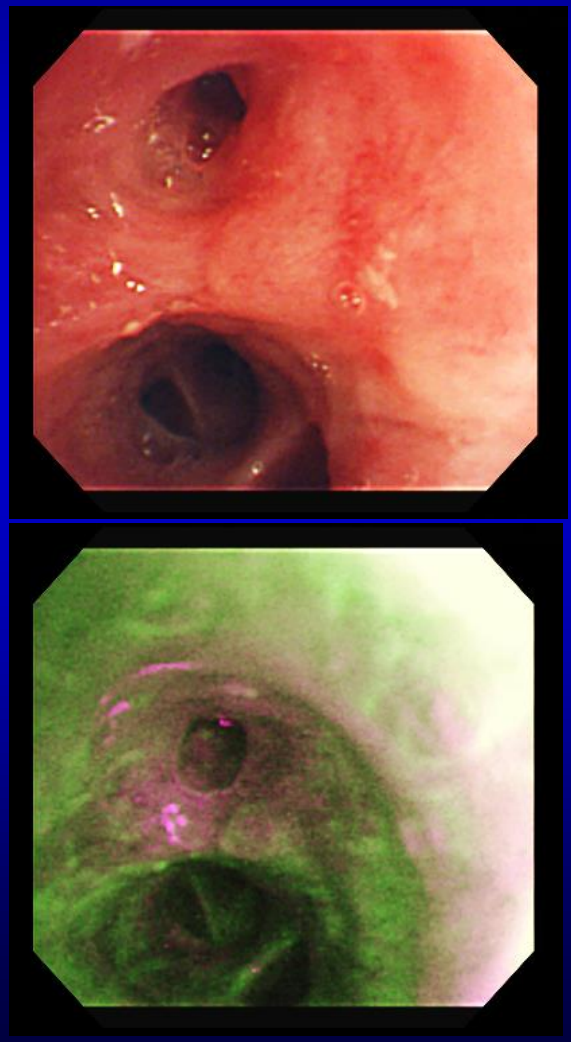
Screening and early detection > endoscopy

- Central endobronchial pre-invasive/early invasive lesions
  - not detected by spiral CT
  - standard white light videobronchoscopy (WLB), complemented autofluorescence bronchoscopy (AFB)
    - pooled relative sensitivity of AFB + WLB versus WLB was 2.04 (95% CI 1.72-2.42)
    - specificity only 65%: quite some 'false-positive' lesions that need extra biopsies



Screening and early detection
> endoscopy: investigations

- **Primary screening**
  - **patients at risk for early intra-epithelial pre-invasive or early invasive lesions**
- **Secondary screening**
  - **search for other synchronous lesions in patients with radiologically visible lung cancer**
  - **search for metachronous pulmonary lesions during follow-up of patients with a curatively treated lung or H&N cancer**
- **Surveillance**
  - **follow-up of patients known with central pre-invasive lesions**

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Screening and early detection
> endoscopy: investigations

Pre-invasive lesion	Regression	Persistence	Progression to CIS/INV
Metaplasia	37-42%	29%	0-9%
Mild/moderate dysplasia	64%	22%	0-11%
Severe dysplasia	52-63%	16%	11-56%
Carcinoma in situ (CIS)	12%	70%	21-67%

Dooms et al, Eur Respir Rev 19: 229-236, 2010

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Leuven, Gothic Town Hall (1448)

Thank you for your kind attention

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