Le dépistage du cancer bronchique

kristiaan.nackaerts@uzleuven.be

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K. Nackaerts - 15 septembre 2014:

Absence de lien d'intérêt déclaré

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Le dépistage du cancer bronchique

- Introduction
- Le scanner thoracique à faible dose
- L'essai NLST
- Autres essais randomisés
- Perspectives
- Thématiques de recherche
- Conclusions

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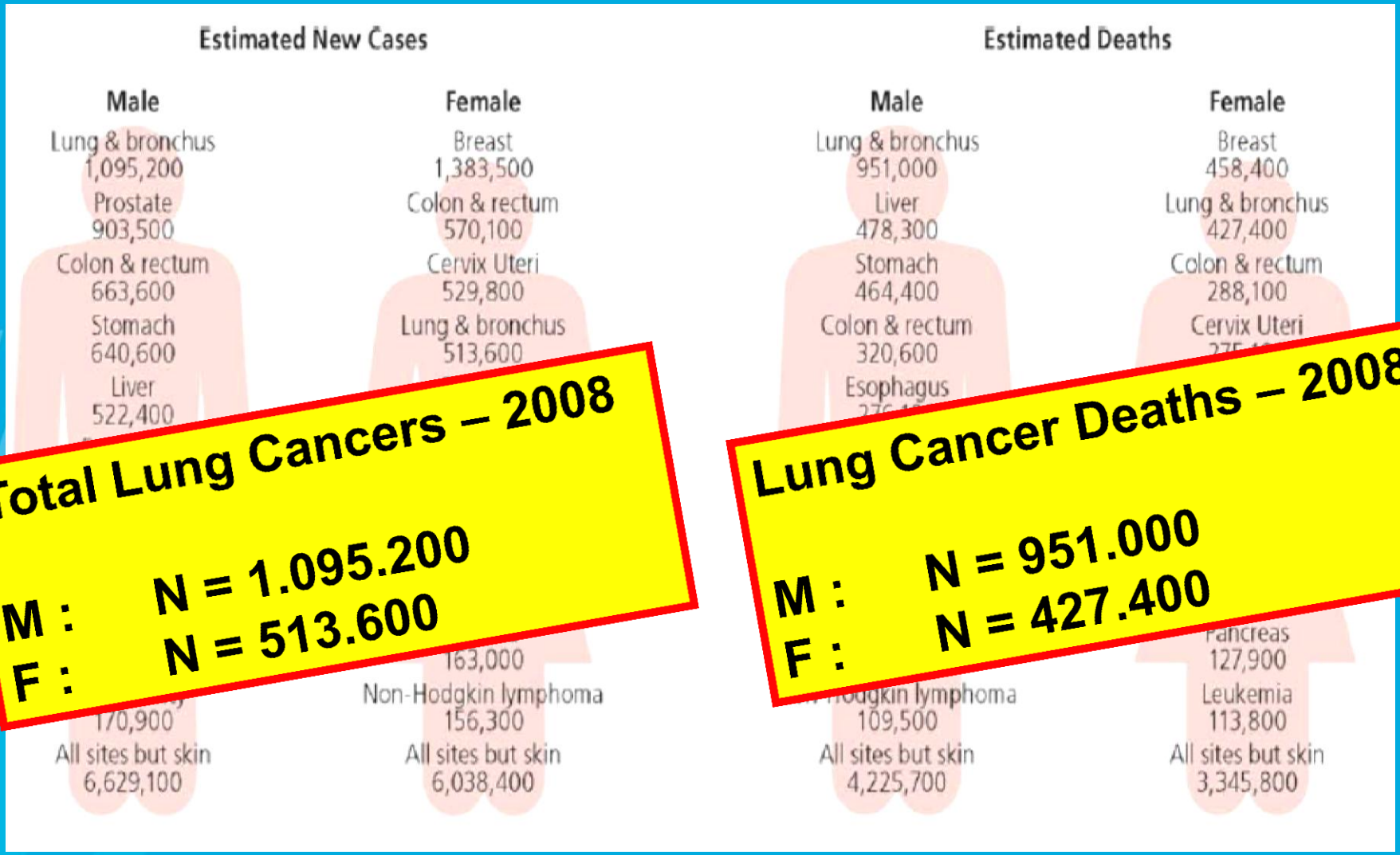
Lung Cancer Screening

- Definition:

"Examining a group of asymptomatic individuals at (highest) risk for lung cancer, to detect an early ('curable') stage of lung cancer, by means of an inexpensive, efficient and safe diagnostic test, in order to significantly reduce lung cancer specific mortality"

New cases of Lung Cancer – Worldwide 2008



Total Lung Cancers – 2008

M : N = 1.095.200
F : N = 513.600

Lung Cancer Deaths – 2008

M : N = 951.000
F : N = 427.400

Jemal A et al CA Cancer J Clin 2011

New cases of Lung Cancer – Worldwide 2012

Estimated numbers (thousands)	Men			Women			Both sexes		
	Cases	Deaths	5-year prev.	Cases	Deaths	5-year prev.	Cases	Deaths	5-year prev.
World	1242	1099	1267	583	491	626	1825	1590	1893
More developed regions	490	417	593	268	210	341	758	626	933
Less developed regions	751	682	674	315	281	286	1066	963	960
WHO Africa region (AFRO)	12	11	10	6	6	5	18	16	15
WHO Americas region (PAHO)	178	149	208	146	113	175	324	262	383
WHO East Mediterranean region (EMRO)	26	23	22	7	6	6	33	29	28
WHO Europe region (EURO)	323	283	343	126	105	133	449	388	476
WHO South-East Asia region (SEARO)	116	104	79	46	42	34	162	146	113
WHO Western Pacific region (WPRO)	588	528	605	251	220	273	839	748	878
IARC membership (24 countries)	514	438	582	279	219	343	794	657	925
United States of America	112	92	140	102	76	128	214	168	269
China	459	422	431	193	175	179	653	597	610
India	54	49	24	17	15	8	70	64	32
European Union (EU-28)	214	185	234	99	82	106	313	268	340

WHO GLOBOCAN 2012 Factsheet Lung Cancer
http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx

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Histology

NSCLC

85-90%

75% stage III-IV

SCLC

10-15%

90% stage III-IV

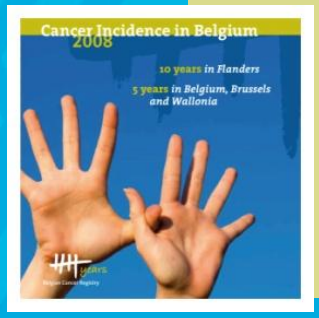
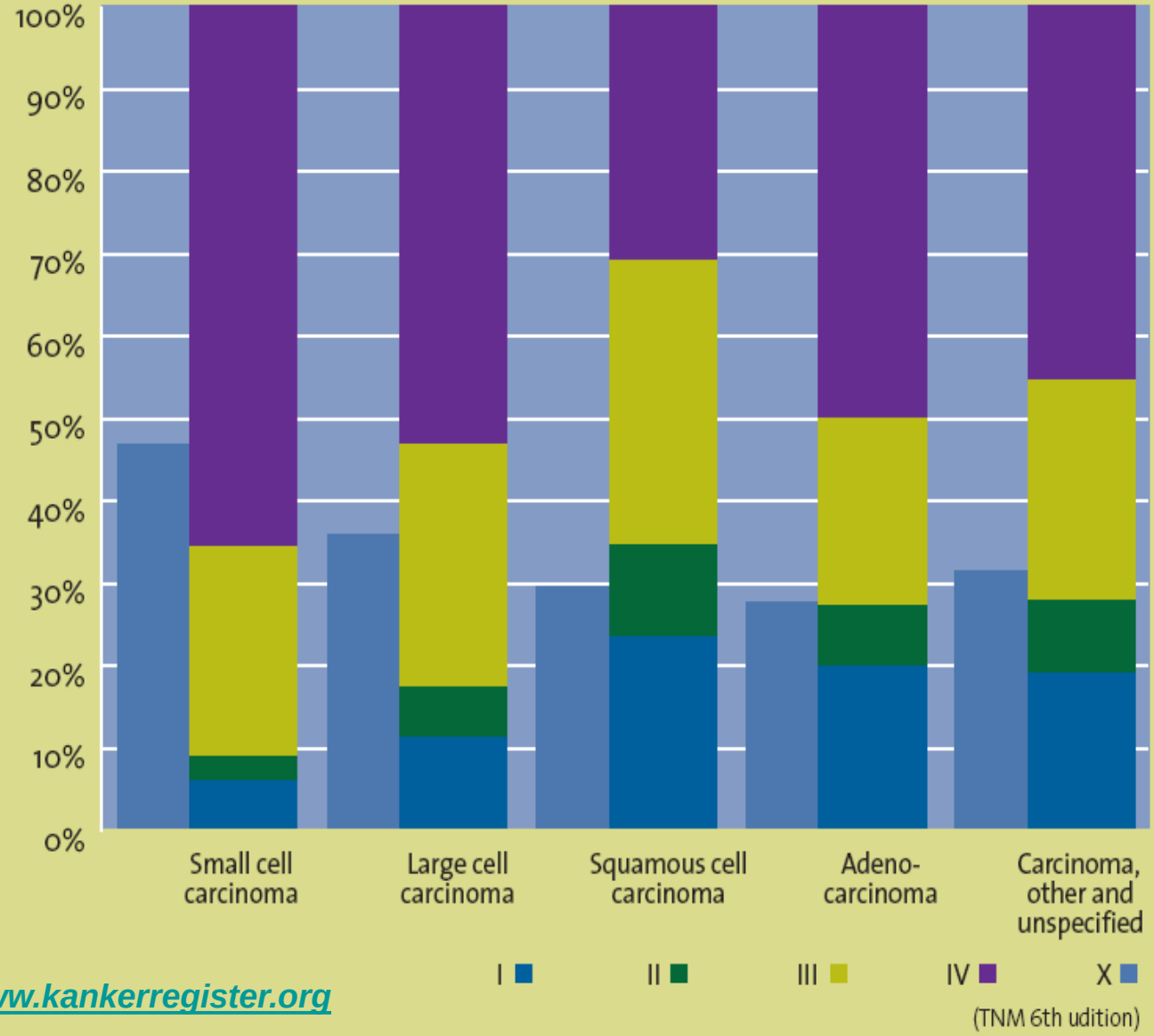


Figure 32 Lung cancer (males & females): Stage by histological type, Belgium 2004-2005



www.kankerregister.org

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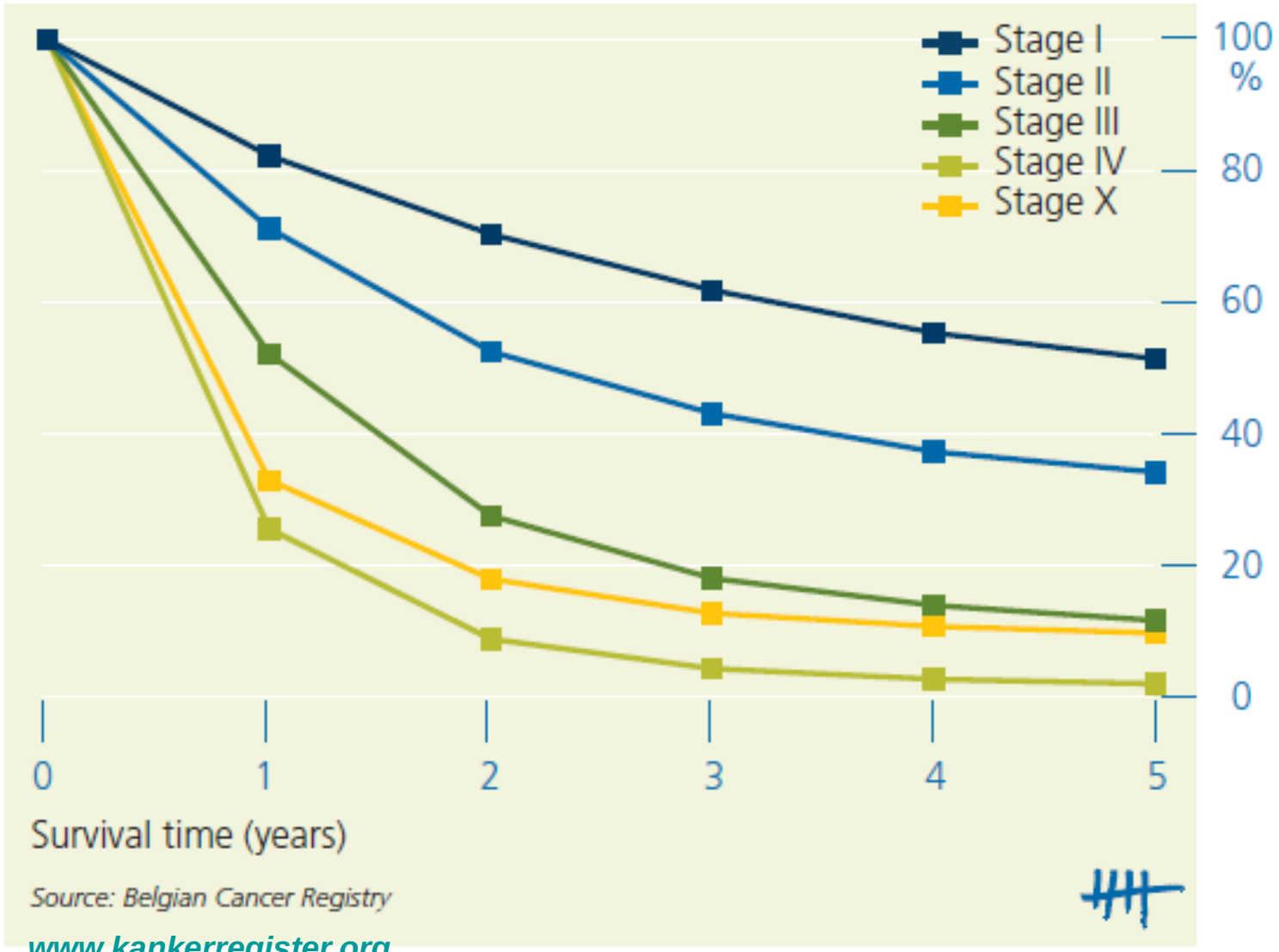
COURS EUROPÉEN INTERUNIVERSITAIRE EN ONCOLOGIE THORACIQUE

FIGURE 70 - LUNG CANCER: RELATIVE SURVIVAL BY STAGE IN MALES (BELGIUM, 2004-2008)



Source: Belgian Cancer Registry

www.kankerregister.org

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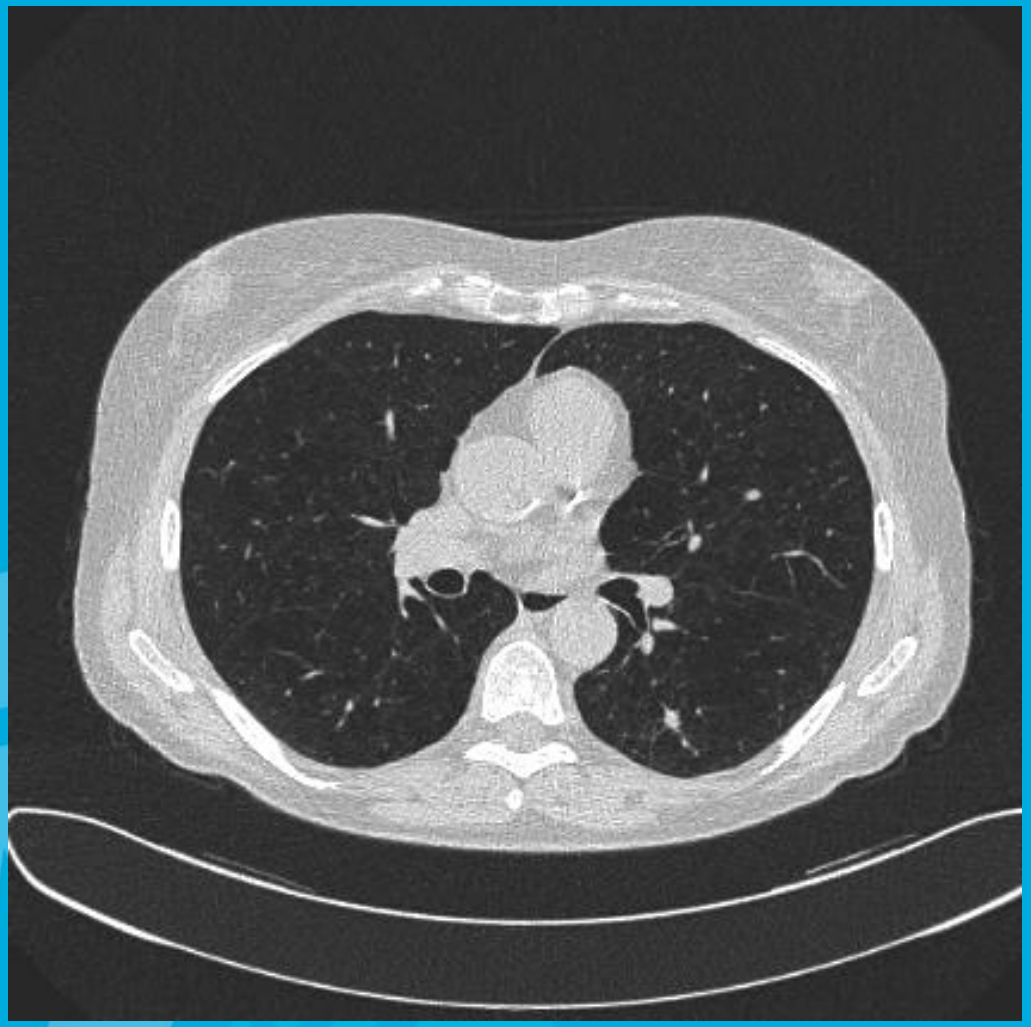

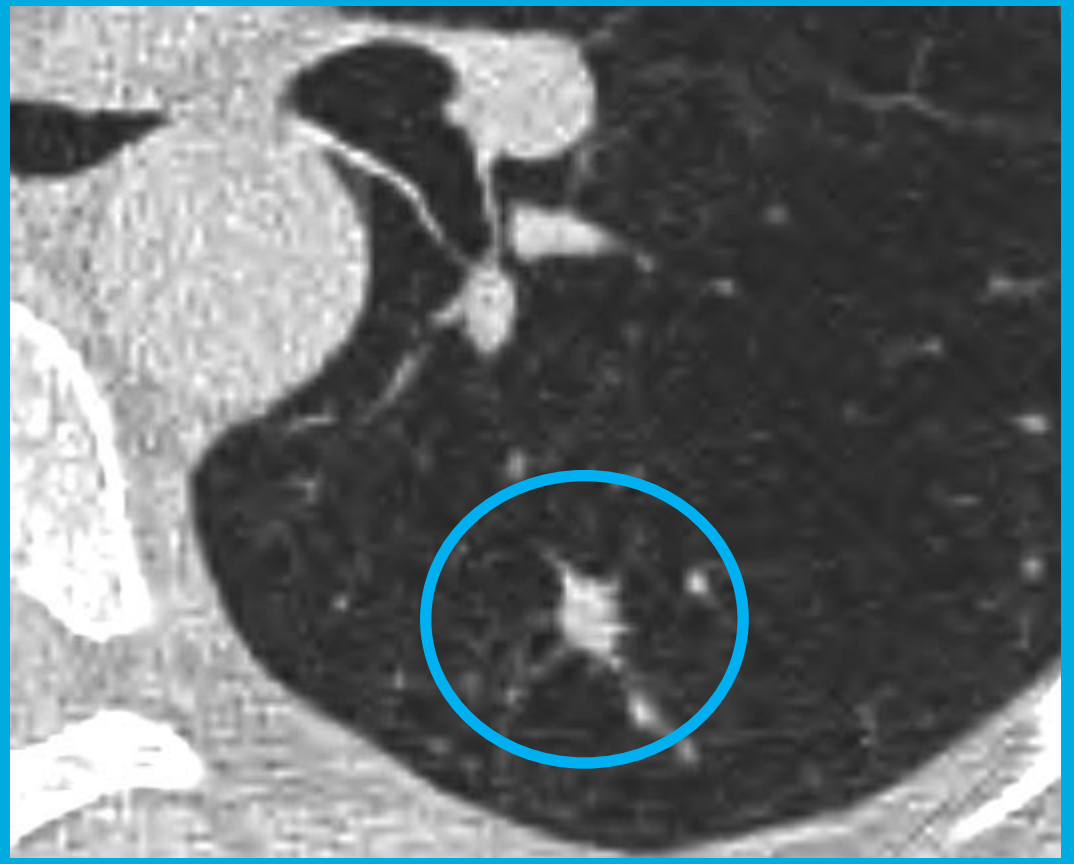

NELSON
19/8/11: Lesion LLL 199mm³, new !

Role of Low Dose Chest CT scan (LDCT)

- Chest X-Ray Screening RCT trials negative
- Low Dose Multidetector Chest CT scan more performant than Chest X-ray[1]
- Data from different large Cohort Trials
- Higher number of lung cancers detected[2]
- Higher number of LC cases in early ('resectable') stages
- High 5- and 10-YSR (*I-ELCAP trial*) for stage I LC cases[3]
- Low radiation exposure[4]

[1]McMahon PM et al BMJ 2007
[2]Henschke CI et al Lancet 1999
[3]I-ELCAP International Investigators NEJM 2006
[4]Mascalchi M et al Br J Radiol 2011

Low dose spiral CT screening

Table 1 One-arm studies

Institution	Year started	Patients enrolled	Age (years)	Percentage smokers/ex smokers	Positive screen (baseline) (%)	Lung cancer (% screened baseline)	Stage I (% lung cancer – % patients enrolled)	Adenocarcinoma (% lung cancer)
ELCAP US [12,13]	1992	1000	>60	100	23.3	2.7	88 – 2.3	78
I-ELCAP International [14]	1993	31 567	61[a]	87	NA.	1.3	85 – 1.1	76
ALCA Japan [15]	1993	1611	>40	86	11.5	0.8	77 – 0.7	77
University Munster, Germany [16,17]	1995	817	>40	100	43	2.1	56 – 0.9	45
Shinshu University, Japan [18,19]	1996	5483	>40	46	5.1	0.4	100 – 0.4	83
Finnish Institute of Occupational Health, Finland [20,21]	1998	602	<75	100	18.4	0.8	0	40
Mayo Clinic, US [22–24]	1998	1520	>50	100	51	2.0	69[d] – 0.9	77
Moffit Cancer Center, US[b]	1998	1151	62[a]	100[c]	NA	3.6	76[e] – 3.3	NA
Hitachi Healthcare Center, Japan [25]	1999	7956	>50	62	6.8	0.4	86 – 0.4	95
PALCAD, Ireland [26,27]	2000	449	>50	100	24	0.4	50 – 0.2	NR
University of Milano Italy [28]	2000	1035	>50	100	5.9[f]	1.1	55 – 0.6	91
Nuclear fuel workers, US [29]	2000	3598	>40	66	32	0.6	NA – 0.3	NR
NY-ELCAP, US [30]	2000	6295	66[a]	100	14	1.6	88 – 1.4	67
PLuSS, US [31]	2002	3642	>50	100	41	1.5	57 – 0.9	NA

Lopes Pegna AL, Picozzi G Curr Opin Pul Med 2009

Survival of Patients with Stage I Lung Cancer Detected on CT Screening

The International Early Lung Cancer Action Program Investigators*

Table 3. Types of Cancer among 412 Participants with Clinical Stage I Lung Cancer Detected on Baseline or Annual CT Screening.

Type of Cancer	Diagnosed on Baseline Screening (N = 348)	Diagnosed on Annual Screening (N = 64)
	no. of participants	
Adenocarcinoma		
Bronchioloalveolar subtype	20	1
Other subtypes	243	30
Squamous cell	45	14
Adenosquamous	3	0
Non–small-cell*	5	2
Neuroendocrine		
Atypical carcinoid	2	1
Large cell	15	8
Small cell	9	7
Other	6	1

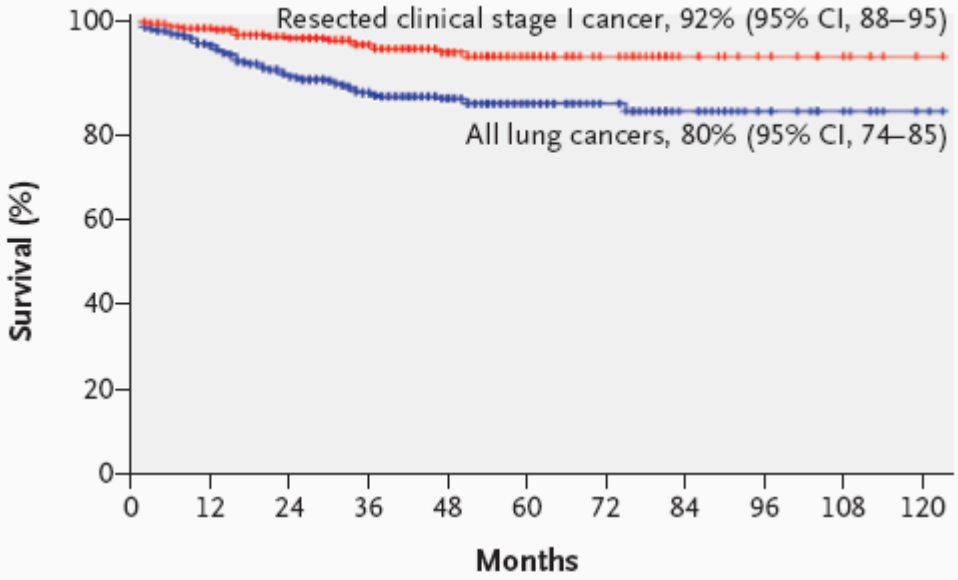

Figure 2. Kaplan–Meier Survival Curves for 484 Participants with Lung Cancer and 302 Participants with Clinical Stage I Cancer Resected within 1 Month after Diagnosis.

The diagnoses were made on the basis of CT screening at baseline combined with cycles of annual CT.

I-ELCAP International Investigators NEJM 2006

LDCT: need for RCTs

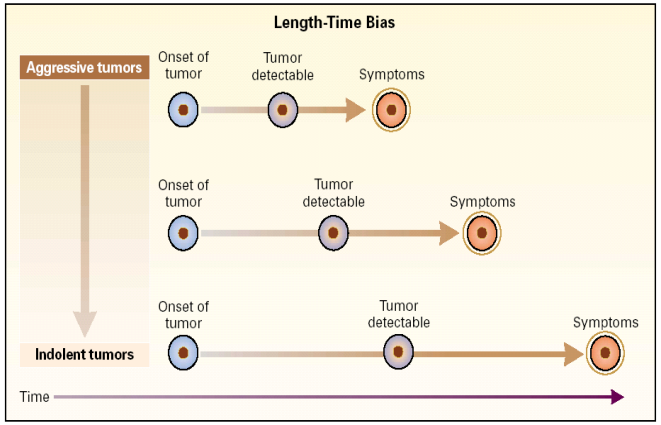

Figure 2. Length-Time Bias.
The probability of detecting disease is related to the growth rate of the tumor. Aggressive, rapidly growing tumors have a short potential screening period (the interval between possible detection and the occurrence of symptoms). Thus, unless the screening test is repeated frequently, patients with aggressive tumors are more likely to present with symptoms. More slowly growing tumors have a longer potential screening period and are more likely to be detected when they are asymptomatic. As a result, a higher proportion of indolent tumors is found in the screened group, causing an apparent improvement in survival.

→ **Biases?**

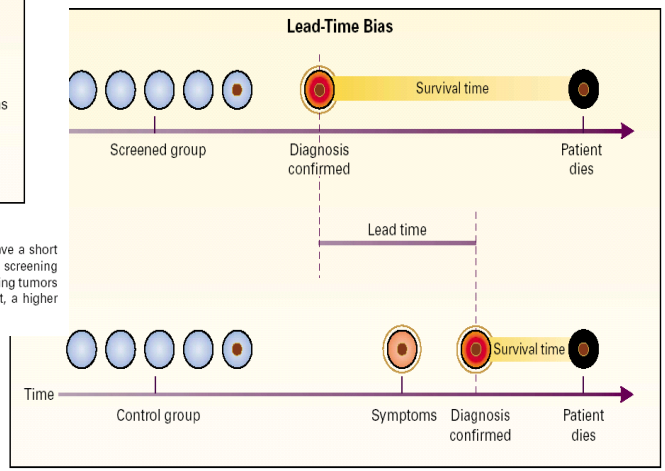

Figure 1. Lead-Time Bias.
In the example shown, the diagnosis of disease is made earlier in the screened group, resulting in an apparent increase in survival time (lead-time bias), although the time of death is the same in both groups.

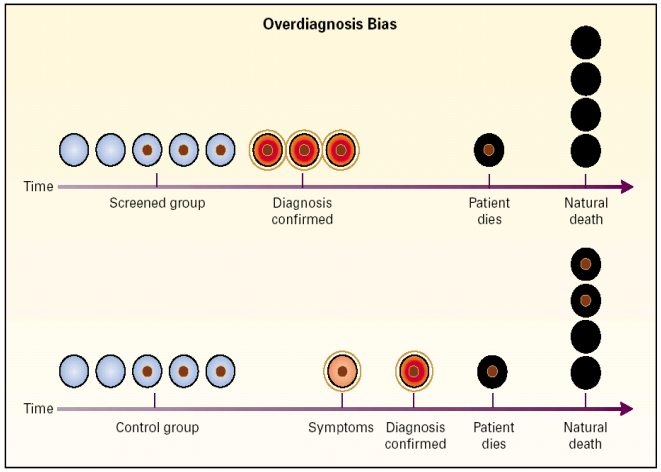

Figure 3. Overdiagnosis Bias.
Overdiagnosis bias is an extreme form of length-time bias. The detection of very indolent tumors in the screened group produces apparent increases in the number of cases of lung cancer (three in the screened group in the figure and one in the control group) and in survival (two of three patients in the screened group were treated and died of natural causes, without evidence of disease [66 percent survival], and the one patient in the control group did not survive [0 percent survival]), with no effect on mortality (one death from lung cancer in each group). Two patients in the control group died with undiagnosed lung cancer that did not affect their natural life span.

→ **LC Specific Mortality reduction?**

Patz EF Jr et al NEJM 2000

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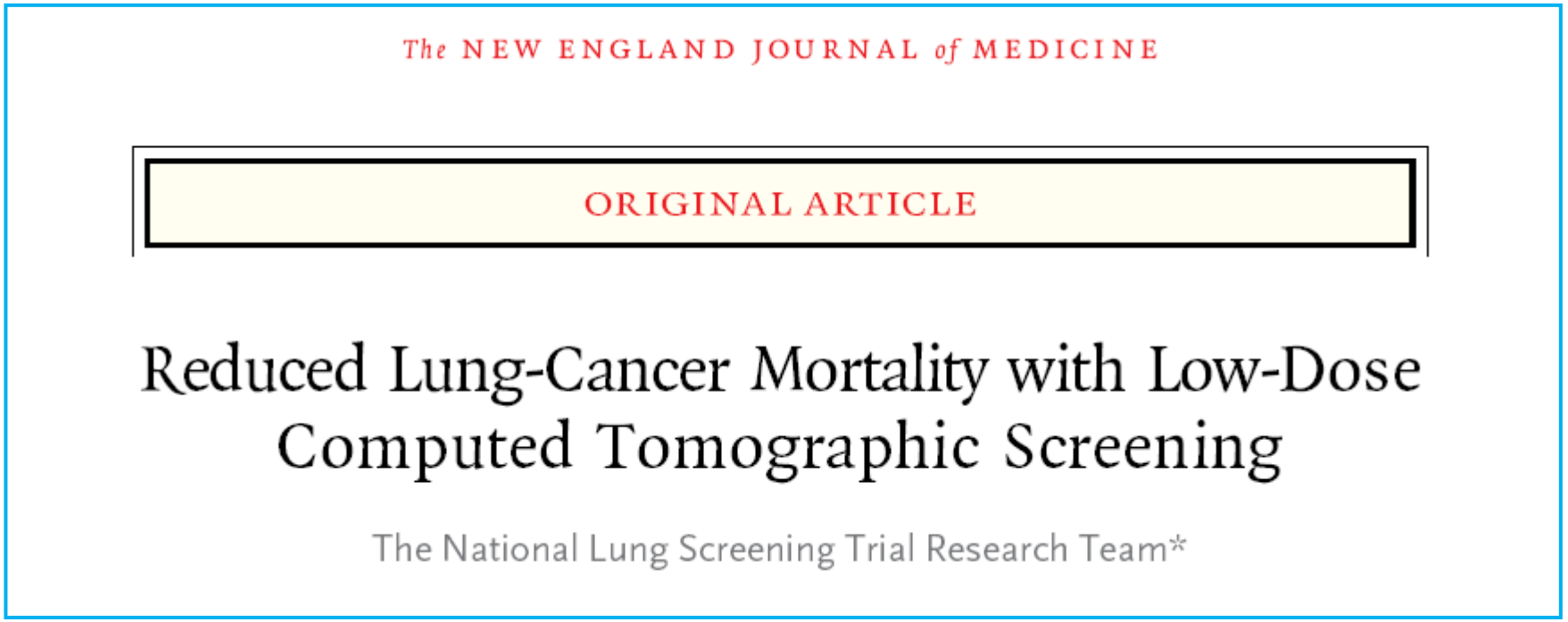
LDCT: National Lung Screening Trial (NLST)

… first positive lung cancer RCT screening trial ever !



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

Aberle DR et al NEJM 2011

LDCT: National Lung Screening Trial (NLST)

Table 1. Selected Baseline Characteristics of the Study Participants.*

Characteristic	Low-Dose CT Group (N = 26,722)	Radiography Group (N = 26,732)
	number (percent)	
Age at randomization		
<55 yr†	2 (<0.1)	4 (<0.1)
55–59 yr	11,440 (42.8)	11,420 (42.7)
60–64 yr	8,170 (30.6)	8,198 (30.7)
65–69 yr	4,756 (17.8)	4,762 (17.8)
70–74 yr	2,353 (8.8)	2,345 (8.8)
≥75 yr†	1 (<0.1)	3 (<0.1)
Sex		
Male	15,770 (59.0)	15,762 (59.0)
Female	10,952 (41.0)	10,970 (41.0)

Aberle DR et al NEJM 2011

LDCT: National Lung Screening Trial (NLST)

Table 2. Results of Three Rounds of Screening.*

Screening Round	Low-Dose CT				Chest Radiography			
	Total No. Screened	Positive Result	Clinically Significant Abnormality Not Suspicious for Lung Cancer	No or Minor Abnormality	Total No. Screened	Positive Result	Clinically Significant Abnormality Not Suspicious for Lung Cancer	No or Minor Abnormality
			no. (% of screened)				*no. (% of screened)*	
T0	26,309	7191 (27.3)	2695 (10.2)	16,423 (62.4)	26,035	2387 (9.2)	785 (3.0)	22,863 (87.8)
T1	24,715	6901 (27.9)	1519 (6.1)	16,295 (65.9)	24,089	1482 (6.2)	429 (1.8)	22,178 (92.1)
T2	24,102	4054 (16.8)	1408 (5.8)	18,640 (77.3)	23,346	1174 (5.0)	361 (1.5)	21,811 (93.4)

* The screenings were performed at 1-year intervals, with the first screening (T0) performed soon after the time of randomization. Results of screening tests that were technically inadequate (7 in the low-dose CT group and 26 in the radiography group, across the three screening rounds) are not included in this table. A screening test with low-dose CT was considered to be positive if it revealed a nodule at least 4 mm in any diameter or other abnormalities that were suspicious for lung cancer. A screening test with chest radiography was considered to be positive if it revealed a nodule or mass of any size or other abnormalities suggestive of lung cancer.

→ **Positive pulmonary nodule: diameter of > 4mm**

Aberle DR et al NEJM 2011

LDCT: National Lung Screening Trial (NLST)

Table 3. Diagnostic Follow-up of Positive Screening Results in the Three Screening Rounds.*

Variable	Low-Dose CT				Chest Radiography			
	T0	T1	T2	Total	T0	T1	T2	Total
	number (percent)							
Total positive tests	7191 (100.0)	6901 (100.0)	4054 (100.0)	18,146 (100.0)	2387 (100.0)	1482 (100.0)	1174 (100.0)	5043 (100.0)
Lung cancer confirmed	270 (3.8)	168 (2.4)	211 (5.2)	649 (3.6)	136 (5.7)	65 (4.4)	78 (6.6)	279 (5.5)
Lung cancer not confirmed†	6921 (96.2)	6733 (97.6)	3843 (94.8)	17,497 (96.4)	2251 (94.3)	1417 (95.6)	1096 (93.4)	4764 (94.5)
Positive screening results with complete diagnostic follow-up information	7049 (100.0)	6740 (100.0)	3913 (100.0)	17,702 (100.0)	2348 (100.0)	1456 (100.0)	1149 (100.0)	4953 (100.0)

"… no specific evaluation approach (for screen-detected nodules) was mandated…"

Aberle DR et al NEJM 2011

LDCT: National Lung Screening Trial (NLST)

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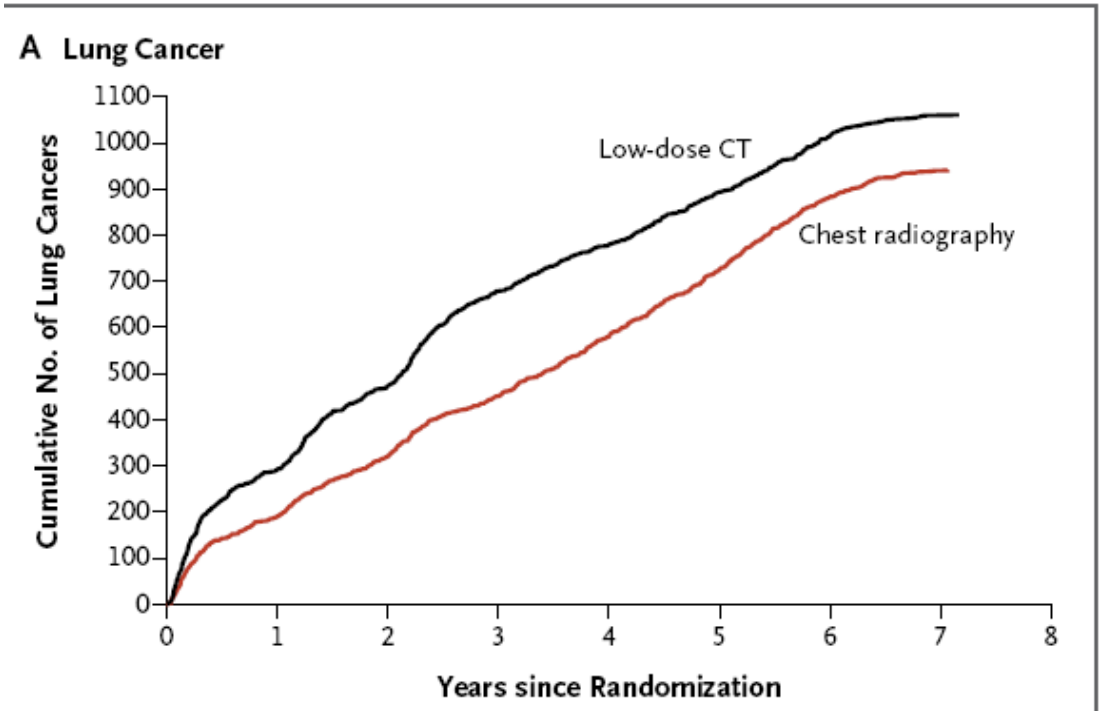
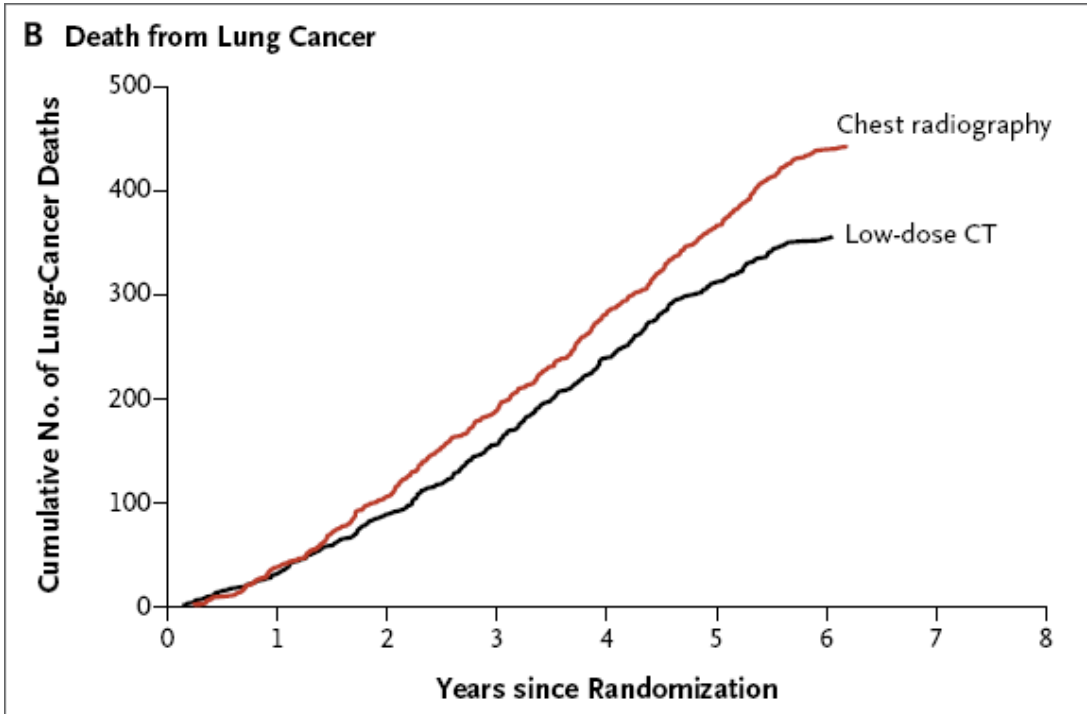
- Prevalence (T0): 1,1% vs 0,7% (CT vs CXR)
- Incidence (T1-T2): 0,7%-0,9% vs 0,5-0,55% (CT vs CXR)
- Adenoca; stage I 63% (CT arm); 92.5% surgically treated

Aberle DR et al NEJM 2011

LDCT: National Lung Screening Trial (NLST)





Total number of deaths due to lung cancer :
247 vs 309 deaths/100.000 pers.yrs (CT vs RX group)
→ relative reduction in LC mortality of 20.0% (95%CI, 6.8 to 26.7; P=0.004)

Number Needed to Screen with LDCT :
320 (to prevent 1 death)

Aberle DR et al NEJM 2011

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LDCT: European RCTs

	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
Recruitment period	2002-2004	2003-2006	2004-2006	2004-2006	2001-2006
Age range (year)	55-74	50-75	50-70	55-69	60-74
Smoking history [1]	≥30/<15	>15/<10	≥20/<10	≥20/<10	≥20/<10
Male/Female	M/F	M/F	M/F	M/F	M
Control arm	Chest X-ray	Usual care	Usual care	Usual care	Usual care [2]
Screening rounds	3	4	5	4	5
Interval (years) [3]	1,2,3	1,2,4,6.5	1,2,3,4,5	1,2,3,4	1,2,3,4,5
Nodule evaluation	2D	2D,3D	2D,3D	2D	2D

Adapted from: Vansteenkiste J et al Ann Oncol 2012

LDCT: European RCTs

	NLST	NELSON	DLST	ITALUNG	DANTE
Control arm	Chest X-ray	Usual care	Usual care	Usual care	Usual care [2]
Screening rounds	3	4	5	4	5
Interval (years) [3]	1,2,3	1,2,4,6.5	1,2,3,4,5	1,2,3,4	1,2,3,4,5
Nodule evaluation	2D	2D,3D	2D,3D	2D	2D
Prevalence detection (%)	**1.1**	0.9	0.8	1.5	2.19
Incidence detection (%)	**0.8**	0.5	0.67	0.4	4.7
False positives (%) [4]	**23.3**	**1.2**	**1.2**	NR	NR
Mortality reduction [5]	20%	(2016)	(2016)	NR	NR

Adapted from: Vansteenkiste J et al Ann Oncol 2012
Horeweg N et al ERJ 2013;42:1659

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Management of Lung Nodules Detected by Volume CT Scanning

Rob J. van Klaveren, M.D., Ph.D., Matthijs Oudkerk, M.D., Ph.D., Mathias Prokop, M.D., Ph.D., Ernst T. Scholten, M.D., Kristiaan Nackaerts, M.D., Ph.D., Rene Vernhout, M.Sc., Carola A. van Iersel, M.Sc., Karien A.M. van den Bergh, M.Sc., Susan van 't Westeinde, M.D., Carlijn van der Aalst, M.Sc., Erik Thunnissen, M.D., Ph.D., Dong Ming Xu, M.D., Ph.D., Ying Wang, M.D., Yingru Zhao, M.D., Hester A. Gietema, M.D., Ph.D., Bart-Jan de Hoop, M.D., Harry J.M. Groen, M.D., Ph.D., Geertruida H. de Bock, Ph.D., Peter van Ooijen, Ph.D., Carla Weenink, M.D., Johny Verschakelen, M.D., Ph.D., Jan-Willem J. Lammers, M.D., Ph.D., Wim Timens, M.D., Ph.D., Dik Willebrand, M.D., Aryan Vink, M.D., Willem Mali, M.D., Ph.D., and Harry J. de Koning, M.D., Ph.D.

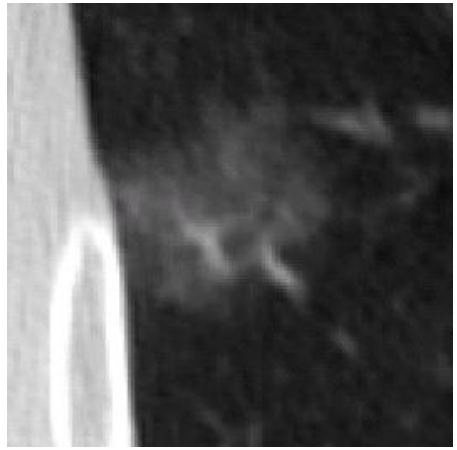
Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial

Nanda Horeweg[1,2], Carlijn M. van der Aalst[1], Rozemarijn Vliegenthart[3], Yingru Zhao[3], Xueqian Xie[3], Ernst Th. Scholten[4], Willem Mali[5], Erik Thunnissen[6], Carla Weenink[7], Harry J.M. Groen[8], Jan-Willem J. Lammers[9], Kristiaan Nackaerts[10], Joost van Rosmalen[1], Matthijs Oudkerk[3] and Harry J. de Koning[1]

Van Klaveren R et al NEJM 2009
Horeweg N et al ERJ 2013;42:1659

NELSON trial

- ✓16-detector CT, 0.7 mm intervals
- ✓Digital workstation Leonardo®
- ✓Lung Care semi-automated Volume measurement



Xu DM et al Lung Cancer 2006;54:177

NELSON
Nederlands-Leuvens Longkanker Screenings Onderzoek

NELSON trial - *nodule classification*

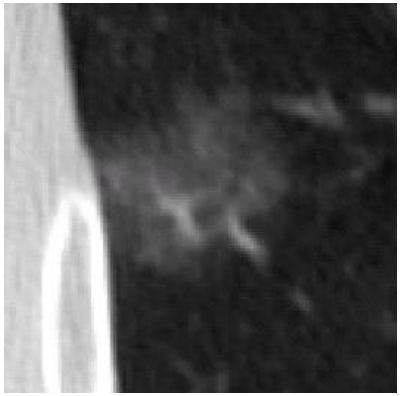


Table 1 NELSON classification of the different non-calcified nodules according to size at baseline screening

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

Xu DM et al Lung Cancer 2006;54:177

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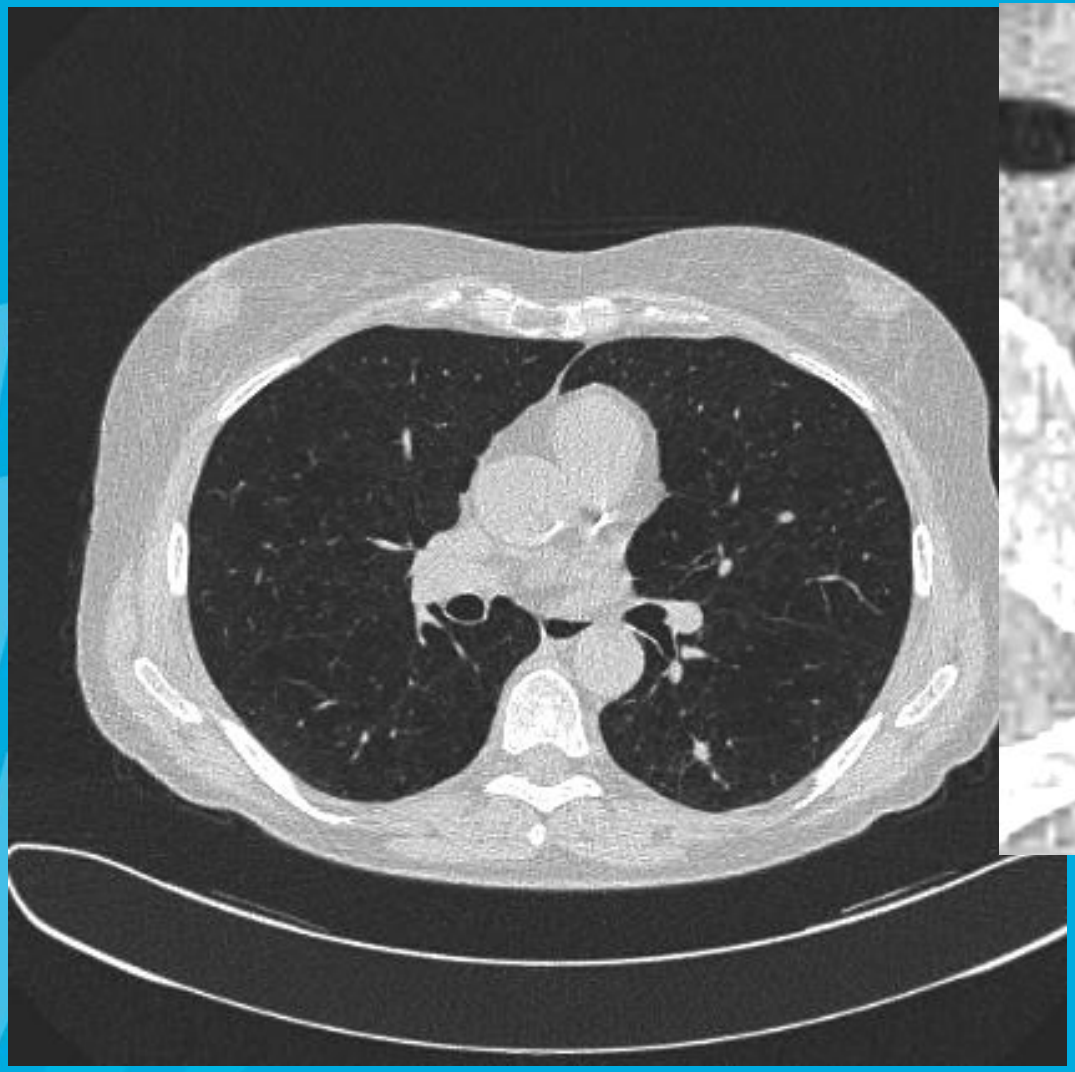
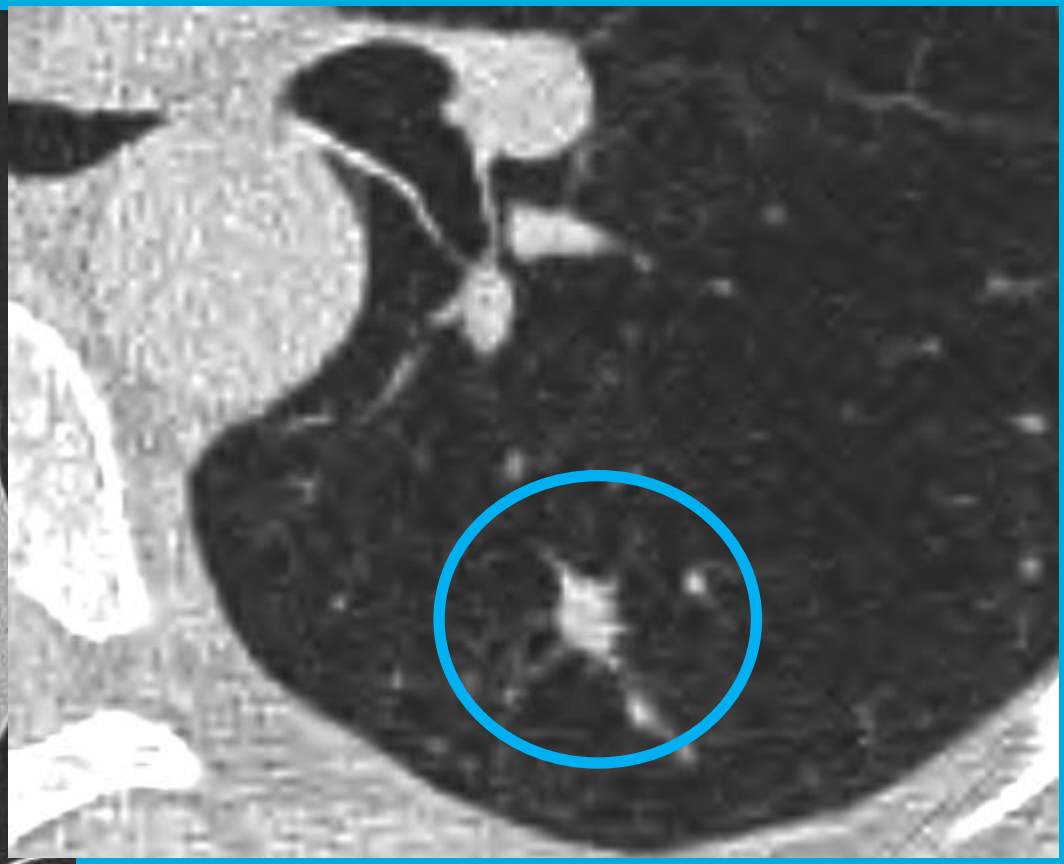
Case

- 4e Round in 2011:





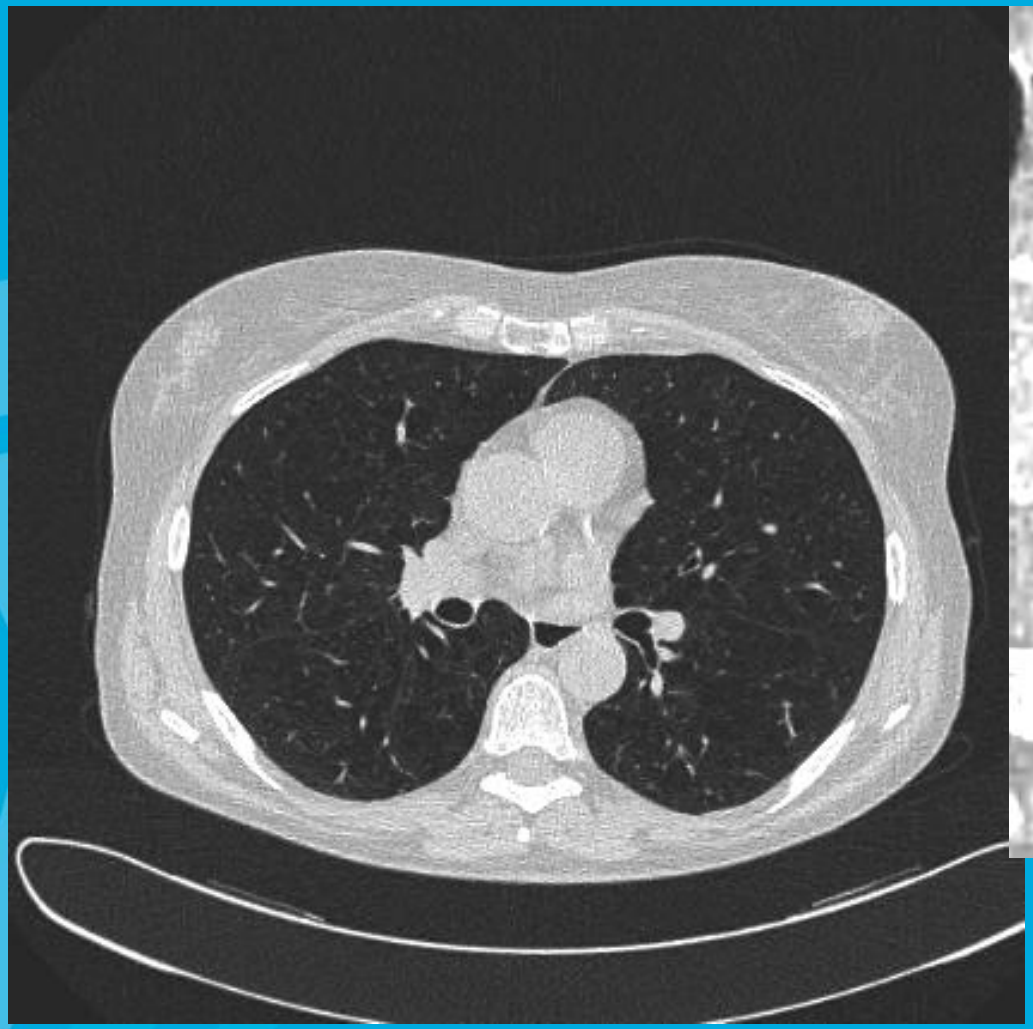
19/8/11: Lesion LLL 199mm³, new !

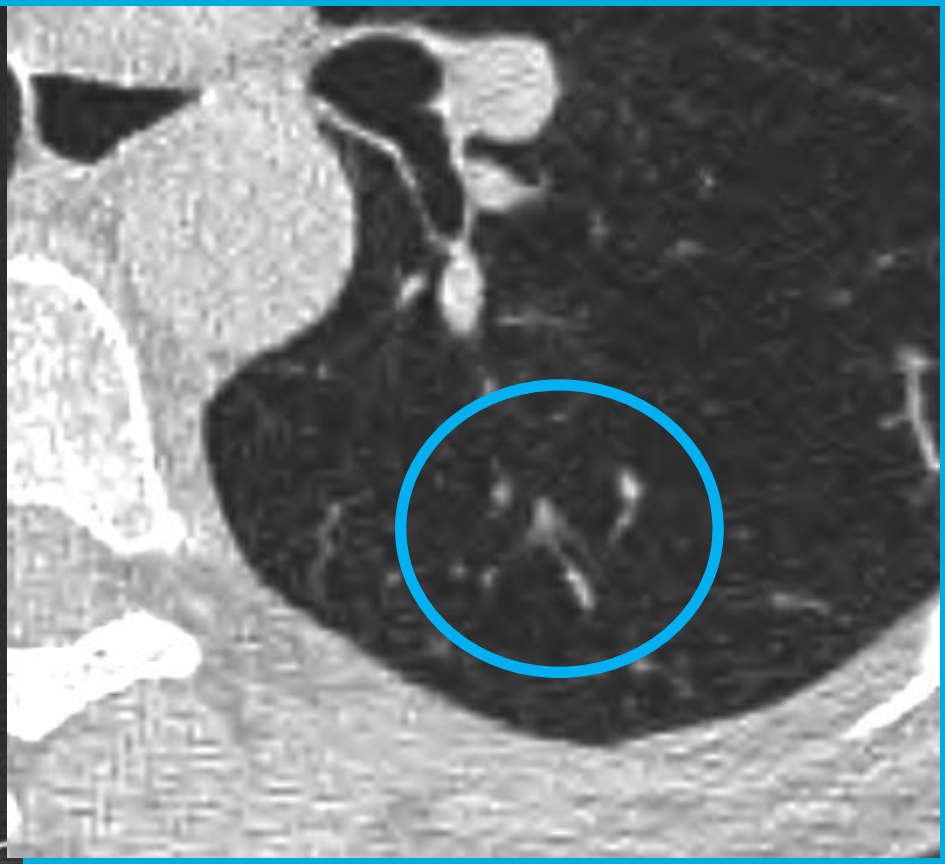
UZ LEUVEN

G.O.L.F. COURS EUROPÉEN INTERUNIVERSITAIRE EN ONCOLOGIE THORACIQUE

Case

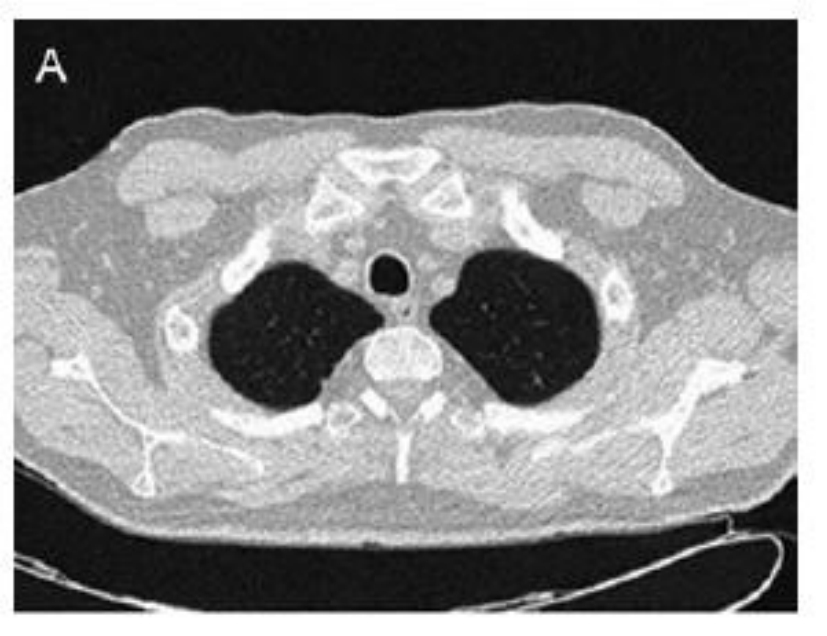
- 4e Round in 2011: Repeat CT-scan

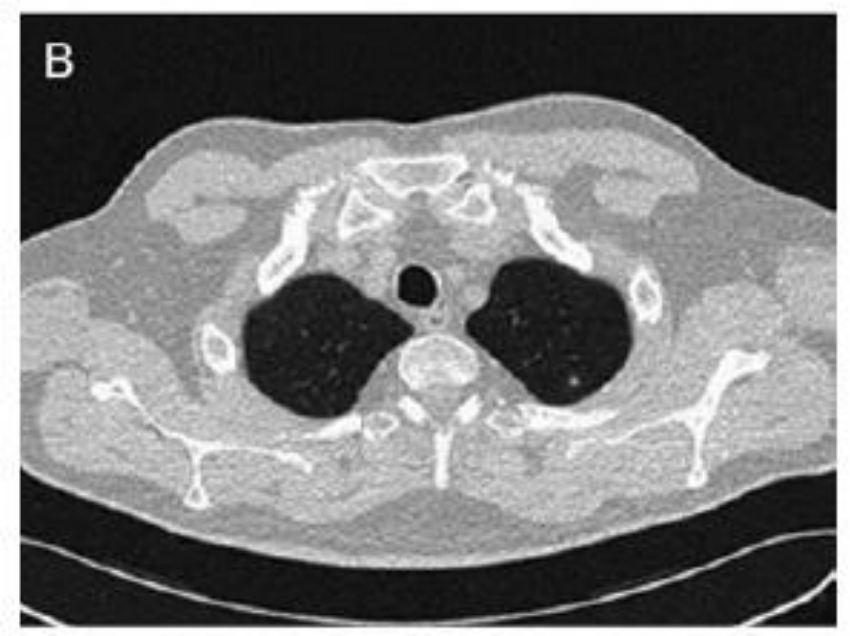




07/10/11: Lesion LLL 22.1 mm³, NEG. !

Case





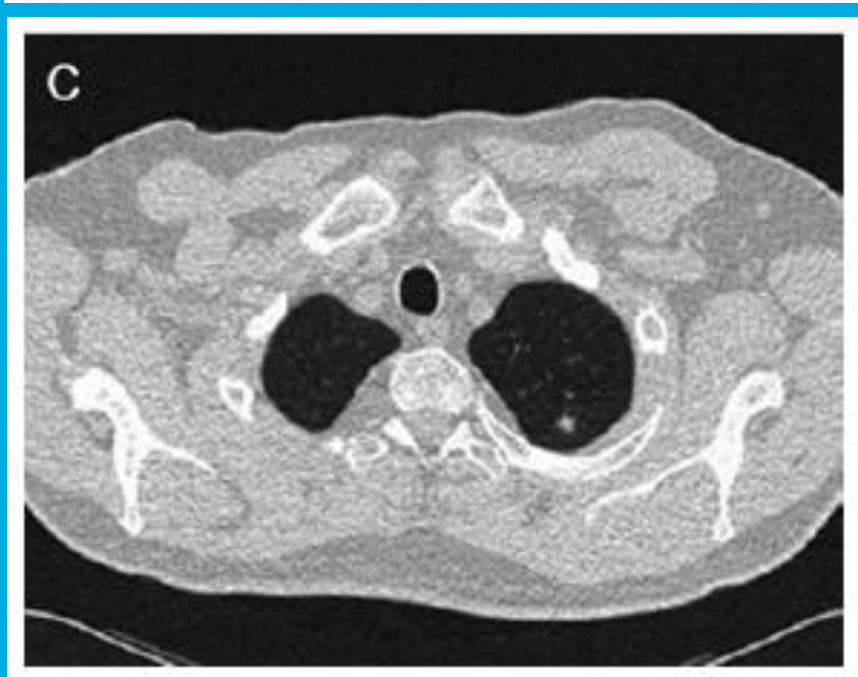


Figure 1. A patient in the screening arm of the NELSON trial. Small nodule in the left upper lobe on CT of the first year (A) and the second year (B). On the third year CT (C), the nodule has grown: the volume is 127 mm^3 and the volume doubling time is <400 days. Nodule growth category is C. Lesion-resected left superior lobectomy: well-differentiated invasive adenocarcinoma pT1N0 (image courtesy KN).

Vansteenkiste J et al Ann Oncol 2012

Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial

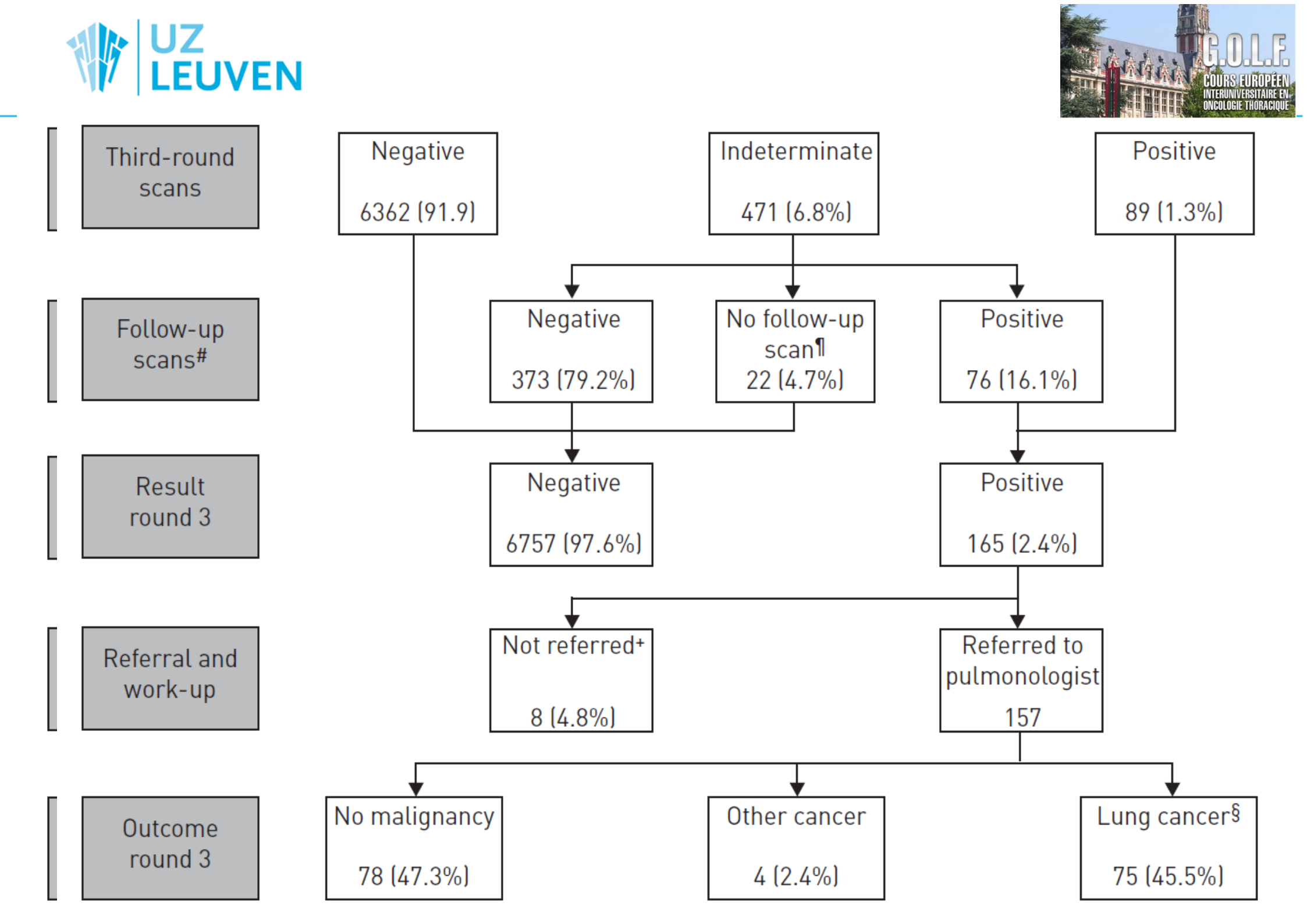
Nanda Horeweg[1,2], Carlijn M. van der Aalst[1], Rozemarijn Vliegenthart[3], Yingru Zhao[3], Xueqian Xie[3], Ernst Th. Scholten[4], Willem Mali[5], Erik Thunnissen[6], Carla Weenink[7], Harry J.M. Groen[8], Jan-Willem J. Lammers[9], Kristiaan Nackaerts[10], Joost van Rosmalen[1], Matthijs Oudkerk[3] and Harry J. de Koning[1]

TABLE 1 Participants' characteristics and comparison stratified by baseline scan result

Characteristics	All screened participants	Baseline scan result negative	Baseline scan result indeterminate	Baseline scan result positive	p-value
Participants	7582	5986	1451	120	
Females	1254 (16.5)	1016 (17.0)	210 (14.5)	22 (18.3)	0.06
Age years median (IQR)	58.0 (8)	57.0 (8)	59.0 (8)	63.0 (10)	<0.001
Current smoker	4215 (55.6)	3315 (55.4)	809 (55.8)	68 (56.7)	0.94
Pack-years median (IQR)	37.8 (19.8)	38.0 (19.8)	38.7 (19.8)	38.7 (24.0)	<0.001

Data are presented as n or n (%), unless otherwise stated. IQR: interquartile range.

Horeweg N et al ERJ 2013;42:1659


Third-round scans
Negative
6362 (91.9)
Indeterminate
471 (6.8%)
Positive
89 (1.3%)
Follow-up scans#
Negative
373 (79.2%)
No follow-up scan¶
22 (4.7%)
Positive
76 (16.1%)
Result round 3
Negative
6757 (97.6%)
Positive
165 (2.4%)
Referral and work-up
Not referred+
8 (4.8%)
Referred to pulmonologist
157
Outcome round 3
No malignancy
78 (47.3%)
Other cancer
4 (2.4%)
Lung cancer§
75 (45.5%)

UZ LEUVEN

Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial

Nanda Horeweg[1,2], Carlijn M. van der Aalst[1], Rozemarijn Vliegenthart[3], Yingru Zhao[3], Xueqian Xie[3], Ernst Th. Scholten[4], Willem Mali[5], Erik Thunnissen[6], Carla Weenink[7], Harry J.M. Groen[8], Jan-Willem J. Lammers[9], Kristiaan Nackaerts[10], Joost van Rosmalen[1], Matthijs Oudkerk[3] and Harry J. de Koning[1]

In this study, we evaluated the performance of the NELSON screening strategy in the first three screening rounds and we assessed the 5.5-year risk of false-positive screenings and screen-detected lung cancer.

If we compare the performance of the NELSON screening strategy with other LDCT screening trials we find notable differences. The percentage of positive scans in our trial (2.0%) was the same as in a Danish trial [10, 13], but substantially lower than in the NLST (24.2%) [5]. Also, the percentage of participants with one or more positive scan was 6.0% in our trial, which is low compared with the 39.1% in the NLST (the percentage in DLCST was not published) [5].

Despite the lower percentage positive screenings, our strategy detected 200 lung cancers in the three screening rounds. As a result, the cumulative lung cancer detection rate (2.6%) was a little higher than in the NLST (649 (2.4%) out of 26 309), but lower than in the DLCST (69 (3.4%) out of 2047) [5, 10]. The latter is probably due to the two additional screening rounds that have been completed in the DLCST.

The predictive value of a positive screen result was higher in the NELSON trial (40.6%) than in both the DLCST (34.8%) and the NLST (3.6%) [5, 10, 13]. Hence, the percentage of false-positive results was 59.4% in the NELSON trial, 65.2% in the DLCST and 96.4% in the NLST. The proportion of false-positive scans out of all scans is 1.2% in the NELSON trial, 1.3% in the DLCST and 23.3% in the NLST [5, 10, 13].

Horeweg N et al ERJ 2013;42:1659

UZ LEUVEN

Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial

Nanda Horeweg[1,2], Carlijn M. van der Aalst[1], Rozemarijn Vliegenthart[3], Yingru Zhao[3], Xueqian Xie[3], Ernst Th. Scholten[4], Willem Mali[5], Erik Thunnissen[6], Carla Weenink[7], Harry J.M. Groen[8], Jan-Willem J. Lammers[9], Kristiaan Nackaerts[10], Joost van Rosmalen[1], Matthijs Oudkerk[3] and Harry J. de Koning[1]

In the NELSON trial, we observed that the ratio between the true-positive and false-positive results improved over the rounds (0.69, 0.72 and 0.83 in rounds one, two and three, respectively). This is probably the result of the possibility in later rounds to compare current with previous images and to calculate VDTs. In the NLST, the true-positive/false-positive ratios were 0.039 in round one, 0.025 in round two and 0.055 in round three (figures in the DLCST were not published) [5]. The improvement in the third round probably results from the fact that only in the third round were stable nodules ⩾4 mm in diameter not classified as positive.

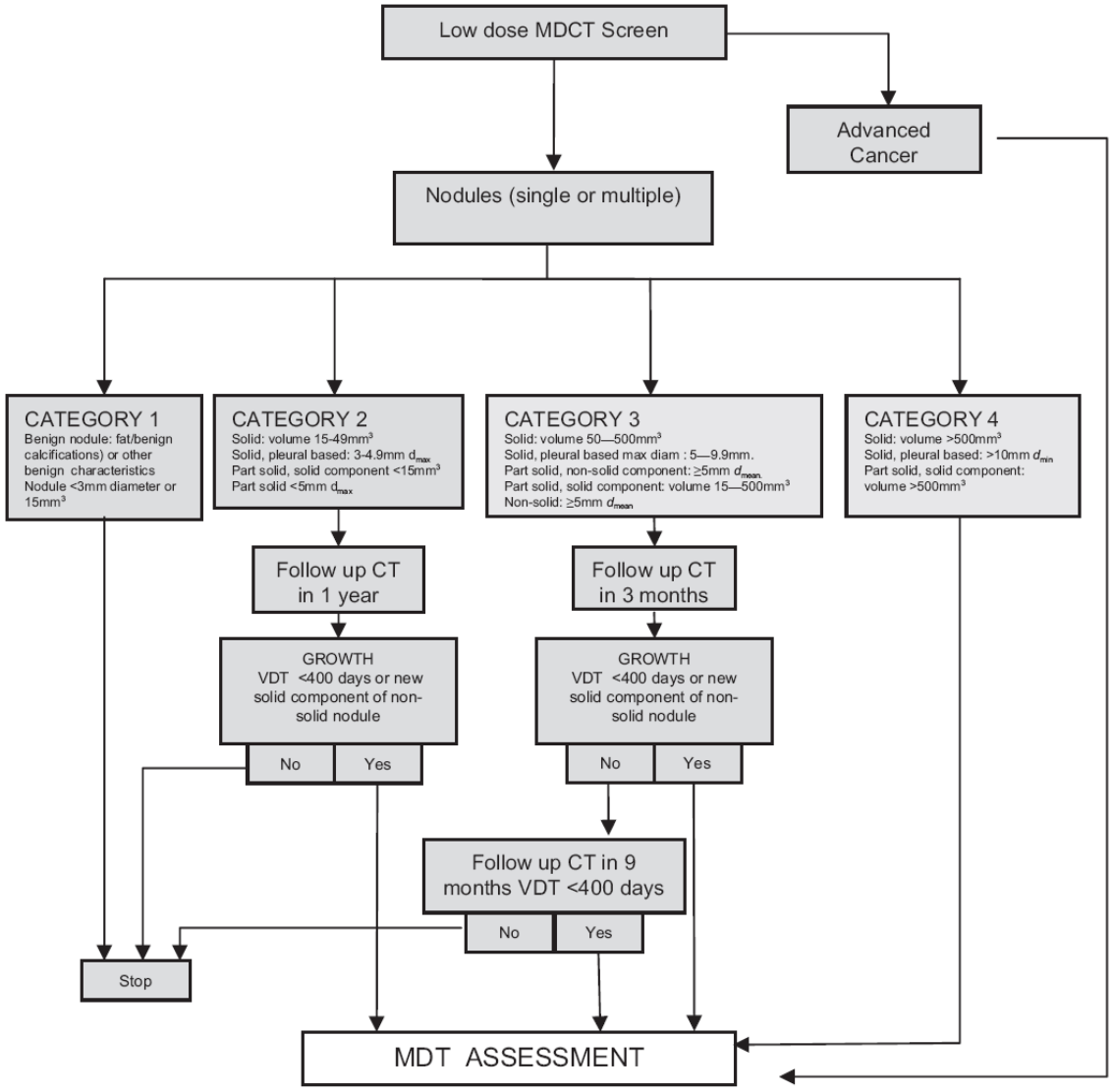
Finally, the number needed to screen for the detection of one lung cancer was 92–133 per round in the NELSON trial, which is a little less than in the other trials (97–147 in the NLST and 116–180 in the DLCST) [5, 10].

Horeweg N et al ERJ 2013;42:1659

LDCT: European RCTs

UKLS

- N: 4000+28000
- Start: 2012
- 7 centres
- LLP risk model: 5% on 5 yr
- Single screen
- 10 y FU
- NELSON nodule management plan



Baldwin DR et al Thorax 2011

ORIGINAL RESEARCH | Annals of Internal Medicine

Predictive Accuracy of the Liverpool Lung Project Risk Model for Stratifying Patients for Computed Tomography Screening for Lung Cancer

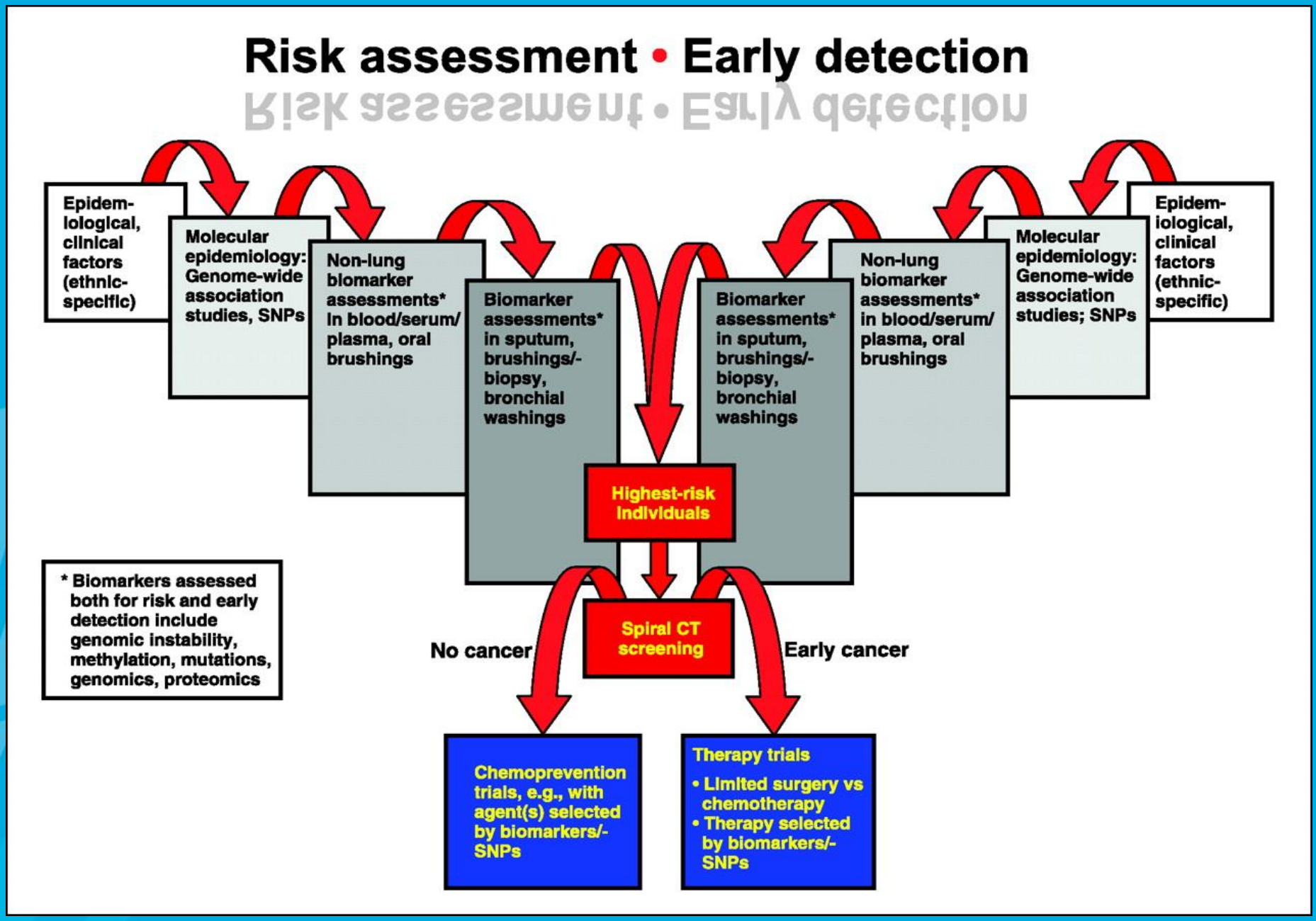
A Case–Control and Cohort Validation Study

Olaide Y. Raji, PhD; Stephen W. Duffy, MSc; Olorunshola F. Agbaje, PhD; Stuart G. Baker, ScD; David C. Christiani, MD, MPH; Adrian Cassidy, PhD; and John K. Field, PhD, FRCPath

Table 1. Risk Factor Distributions and Estimated Model Coefficients From the LLP Case–Control Data*

Variable	Case Patients, *n* (%)	Control Participants, *n* (%)	Odds Ratio (95% CI)	Model Coefficient	
				Full Model	Reduced Model†
Risk factor					
Smoking duration					
Never	25 (5.9)	240 (28.3)	1.00 (reference)	–	–
1–19 y	37 (8.7)	171 (20.2)	2.17 (1.21–3.85)	0.769	0.795
20–39 y	122 (28.6)	249 (29.4)	4.27 (2.62–6.94)	1.452	1.470
40–59 y	227 (53.2)	176 (20.8)	12.27 (7.41–20.30)	2.507	2.536
≥60 y	16 (3.8)	12 (1.4)	15.25 (5.71–40.65)	2.724	2.742
History of pneumonia	97 (22.7)	129 (15.2)	1.83 (1.26–2.64)	0.602	0.592
Asbestos exposure	150 (35.1)	202 (23.8)	1.89 (1.35–2.62)	0.634	–
History of cancer	60 (14.1)	59 (7.0)	1.96 (1.22–3.14)	0.675	0.680
Family history of lung cancer					
None	314 (73.5)	699 (82.4)	1.00 (reference)	–	–
Early onset (age <60 y)	44 (10.3)	40 (4.7)	2.02 (1.18–3.45)	0.703	0.690
Late onset (age ≥60 y)	69 (16.2)	109 (12.9)	1.18 (0.79–1.76)	0.168	0.201
Internal validation					
AUC	–	–	–	0.758	0.753

Raji OY et al Ann Int Med 2012



Field JK, Raji OY F1000 Med Reports 2010

March 2001 - February 2006

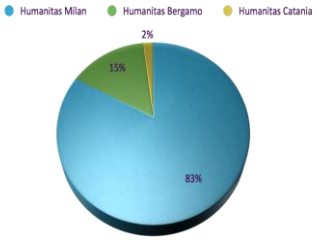
PRE-ASSESSED AND RANDOMIZED N=2811

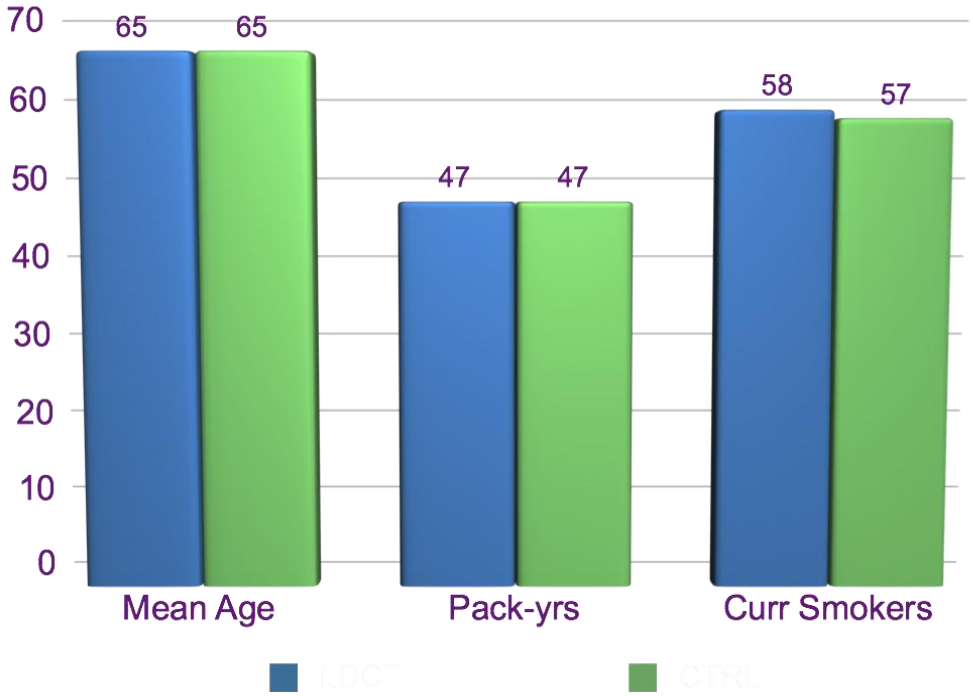
Spiral CT N=1403		Control N=1408
91 declined 46 ineligible	CLINICAL ASSESSMENT	166 declined 46 ineligible
Enrolled in LDCT arm N=1276		Enrolled in CTRL arm N=1196
Chest radiograph and sputum cytology		Chest radiograph and sputum cytology
Baseline LDCT		
4 X annual LDCT + Clinical Review		4 X annual Clinical Review

M. Infante et al. WCLC 2013 O05.01.

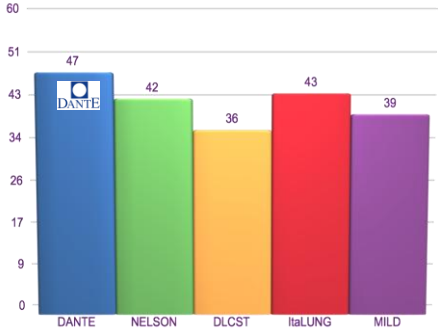
Patients characteristics
and comparisons with other RCTs

DANTE

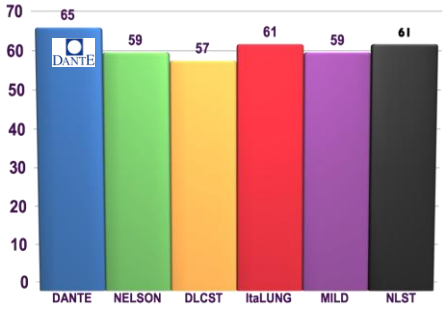




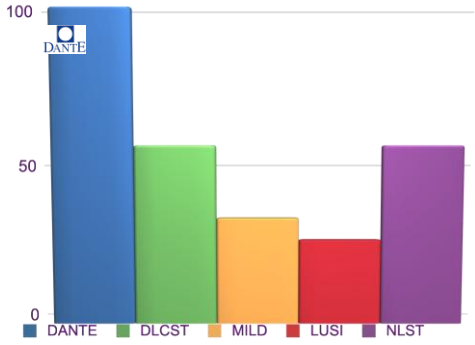
Mean pack-yrs



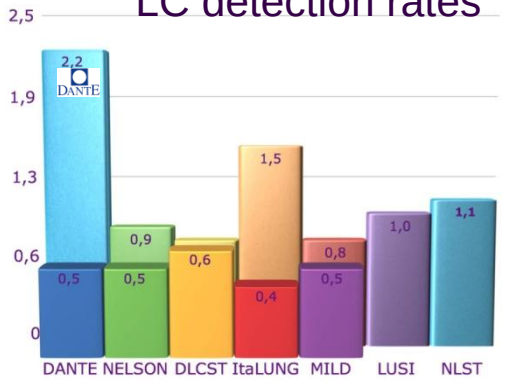
Mean Age



% over 60



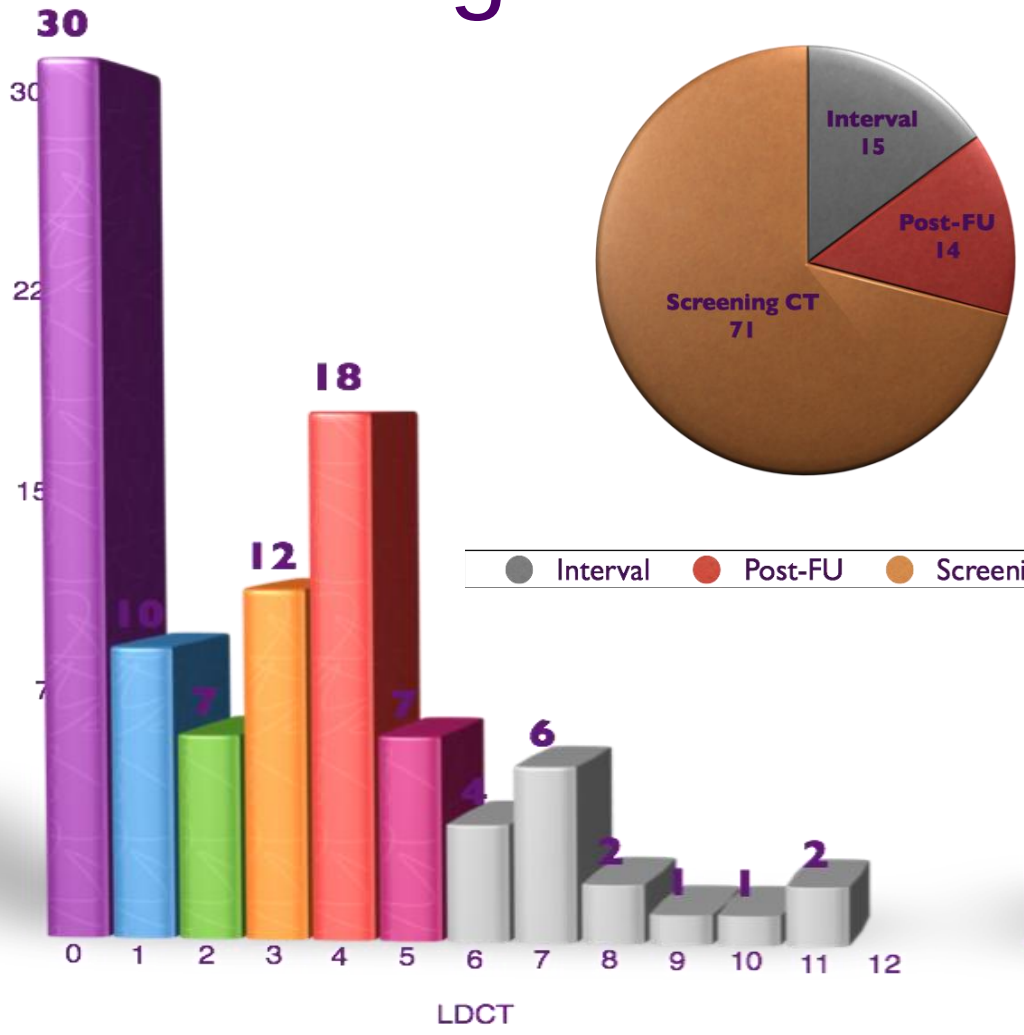
LC detection rates



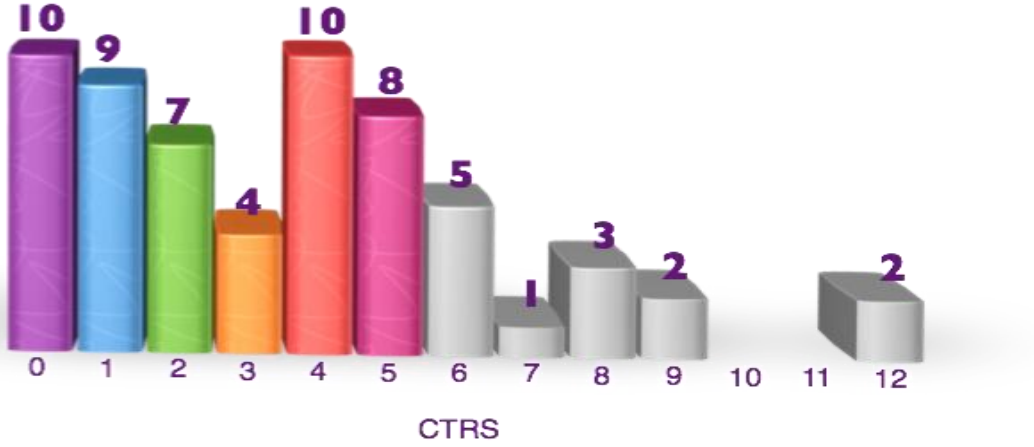
Baseline and round 1

M. Infante et al. WCLC 2013 O05.01.

N° lung cancers diagnosed per year



Interval Post-FU Screening CT



Patients	92
Lung cancers	100
Single Tumor	88
Synchronous	4
Metachronous	8

Patients	60
Lung cancers	61
Single Tumor	59
Synchronous	1
Metachronous	1

M. Infante et al. WCLC 2013 O05.01.

LDCT: European RCTs

Source	Compared With	No. of Participants Screened or Followed Up: LDCT	No. of Participants Screened or Followed Up: Control	Median Follow-up, mo	*P* Value on End Point	Mortality Events, No. (%): LDCT	Mortality Events, No. (%): Control
			Lung Cancer-Specific Mortality				
DANTE,[22] 2009	Usual care	1276	1196	34	.83	20 (1.6)	20 (1.7)
NLST,[23] 2011	Chest radiographs	26 722	26 732	78	.004	356 (1.3)	443 (1.7)
DLCST,[19] 2012	Usual care	2052	2052	58	.06	15 (0.7)	11 (0.5)

Infante M et al Am J Respir Crit Care Med 2009
Saghir Z et al Thorax 2012
Bach PB et al JAMA 2012

UZ LEUVEN

Le dépistage du cancer bronchique

- Introduction
- Le scanner thoracique à faible dose
- L'essai NLST
- Autres essais randomisés
- **Perspectives**
- Thématiques de recherche
- Conclusions

VOLUME 31 · NUMBER 8 · MARCH 10 2013

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Computed Tomography Screening for Lung Cancer: Has It Finally Arrived? Implications of the National Lung Screening Trial

Denise R. Aberle, Fereidoun Abtin, and Kathleen Brown

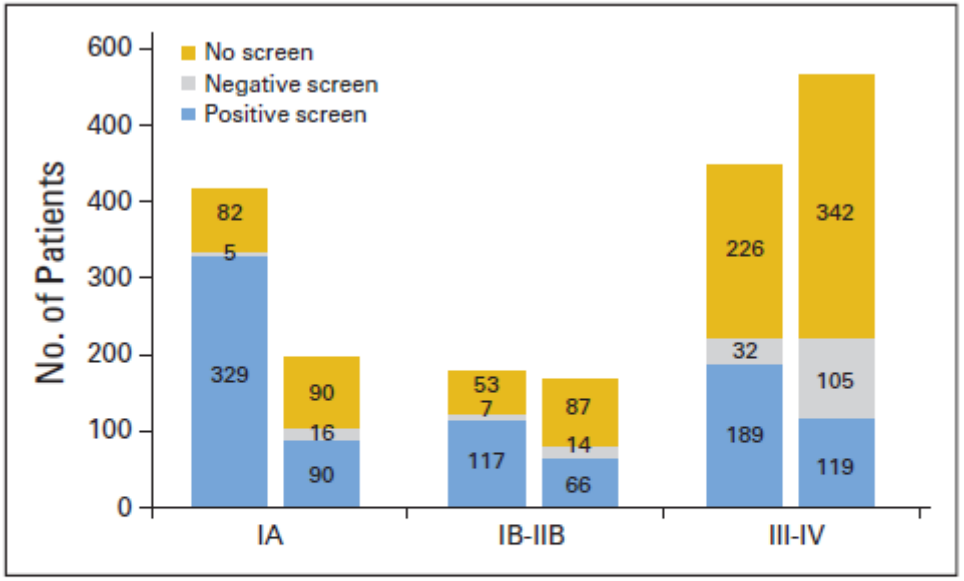


Fig 2. Stage of lung cancers in the two screening arms based on result of screening. Lung cancers are shown as early-stage IA, intermediate-stage IB to IIB, and late-stage III to IV. In each arm, the stages are displayed by screen result, in which lung cancers were diagnosed after a positive screen, after a negative screen, or in participants who received no screen. Ninety percent of lung cancer diagnoses occurring with no screen occurred in the postscreening surveillance period. Lung cancers of unknown stage (n = 32) are excluded.

Aberle et al J Clin Oncol 2013;31:1002-8

LDCT: Implementation: benefits & harms?

- ‘Target’ population (no mass screening)
- Reduced lung cancer mortality
- Cost-effectiveness (?)
- Smoking cessation advice

- QOL
- Psychosocial consequences
- False positives and false negatives (interval cancers)
- Morbidity/Mortality risk
- Radiation exposure risk

NCCN Guideline Lung Cancer Screening v1.2012
Bach PB et al JAMA 2012

UZ LEUVEN

Talking With Your Patients About Screening for Lung Cancer

U.S. Preventive Services TASK FORCE

Inviting asymptomatic individuals for screening and implementing a large-scale screening program should be considered only when the benefits clearly outweigh the harms. Our analysis provides a detailed account of the balance between harms and benefits of annual lung cancer screening to inform individuals, clinicians, and policymakers. But our predictions have some uncertainty and are contingent on high-quality screening, 100% adherence with screening, and closely coordinated follow-up and treatment protocols. Both future providers and possible recipients of lung cancer screening should be fully aware of this and opt for screening only after having been informed about these harms and benefits.

Evidence

This reco … lomized controlled trial to date with more tha… e benefits and harms of screening programs… uded that a reasonable balance of benefits a… rent smokers or have quit within the past 15 y…

…mography Lung Cancer Screening … Study for the U.S. Preventive …

…n ten Haaf, MSc; Vidit N. Munshi, MS; Jihyoun Jeon, PhD; …, Joost van Rosmalen, PhD; Sung Eun Choi, SM; Paul F. Pinsky, PhD; Amy Berrington de Gonzalez, PhD; Christine D. Berg, MD; William C. Black, MD; Martin C. Tammemägi, PhD; William D. Hazelton, PhD; Eric J. Feuer, PhD*; and Pamela M. McMahon, PhD*

www.uspreventiveservicestaskforce.org

De Koning H et al Ann Intern Med 2013 online 31-12-2013

UZ LEUVEN

Talking With Your Patients About Screening for Lung Cancer

U.S. Preventive Services TASK FORCE

Maximizing the Benefits of a Lung Cancer Screening Program

We recognize that the body of evidence on the effectiveness of screening for lung cancer will continue to evolve, which may help the Task Force further clarify its recommendation in the future. What we know now, is that lung cancer screening can save lives and prevent deaths from lung cancer, and that the benefits of screening can be maximized if health care professionals consider the following:

1. **Limiting screening to people who are at high risk.** Based on current evidence, the Task Force recommends that screening be limited to people between 55 and 80 years old, who have a 30-pack-year history of smoking and are current smokers or quit less than 15 years ago. While future research will likely help the USPSTF refine the criteria for screening, possibly removing some people now considered at increased risk and including others who are not currently included, at this time health care professionals should limit screening to those currently defined as being at high risk. Additionally, most trials, including the NLST, only enrolled people who were generally healthy. The benefit of screening may be significantly less in people with serious medical problems and there is no benefit in screening someone for whom treatment is not an option.
2. **Accurately interpreting the images produced from the LDCT.** The evidence on the benefits of lung cancer screening comes from research conducted in large academic medical centers with expertise in diagnosing and managing lung cancer. Those benefits are most likely to be duplicated in clinical settings that have high rates of diagnostic accuracy using LDCT.
3. **Resolving most false-positive results without invasive procedures.** False-positive results occur in a substantial proportion of people screened; 95 percent of all positive screens do not lead to a diagnosis of cancer. To help reduce the harms associated with false-positive test results, health care professionals could consider resolving false-positives with further imaging and watching lesions over time rather than with invasive procedures.

Most importantly, the Task Force recommends that everyone enrolled in a lung cancer screening program receive interventions to help them stop smoking. Most lung cancer deaths cannot be prevented by screening, and smoking cessation remains a critical way to help reduce lung cancer diagnoses and deaths.

UZ LEUVEN

ÉDITORIAL

Vers un dépistage individuel du cancer broncho-pulmonaire en France ? L'avis de l'IFCT, de la SIT et du GOLF

From the NLST randomized trial to the clinic: How should we implement individual lung cancer screening in clinical practice?

S. Couraud[a,*,b], F. Barlési[c], E. Lemarié[d], G. Zalcman[e,f], B. Milleron[g], pour le groupe de travail IFCT/GOLF sur le dépistage du cancer broncho-pulmonaire[1]

"…proposer un dépistage scannographique du cancer bronchopulmonaire en France"

"…réaliser un dépistage individuel opportuniste…"

Couraud S et al Rev Mal Resp 2013;30:15-17

The International Association Study Lung Cancer (IASLC) Strategic Screening Advisory Committee (SSAC) Response to the USPSTF Recommendations

John K. Field, PhD, FRCPath, Denise R. Aberle, MD,† Nasser Altorki, MD,‡ David R. Baldwin, MD, FRCP,§ Carolyn Dresler, MD, MPA,‖ Stephen W. Duffy, MSc,¶ Peter Goldstraw, FRCS,# Fred R. Hirsch, MD, PhD,** Jesper Holst Pedersen, DMsci,†† Harry J. de Koning, MD, PhD,‡‡ James L. Mulshine, MD,§§ Daniel C. Sullivan, MD,‖‖ ıg-Sound Tsao, MD, FRCPC,¶¶ and William D. Travis, MD## on behalf of the International Association for the Study of Lung Cancer Strategic Screening Advisory Committee.*

IASLC Statement

The IASLC has previously supported research into CT screening trials in the light of the public health burden of lung cancer. Each national health service now has an opportunity to decide its own way forward regarding the merits of CT screening based on their interpretation of the existing NLST data and information from other lung cancer screening trials. However, the IASLC makes the following statements: First, the implementation of any screening process should be performed incorporating best practice for screening care in centers that are able to achieve excellence in providing this service and that have a multidisciplinary group of experts focused on this problem. In discussions about screening, for those who have not done so, smoking cessation is the most important measure available to improving overall health outcomes. For former smokers considering lung cancer screening, it is clear that the increased risk of developing lung cancer is diminishing but lifelong.[5]

The IASLC SSAC recommends that the following current issues should be considered by national health service providers as they consider implementing lung cancer screening:

- **Screening selection criteria**
- **Fitness & (max) age of participants**
- **Radiology protocol for nodules**
- **Weighing ‘benefits’ vs ‘harms’**
- **Cost-effectivity analysis**

J Thorac Oncol 2014; 9: 141-3

http://www.uspreventiveservicestaskforce.org/ 31-12-2013

UZ LEUVEN

Le dépistage du cancer bronchique

- Introduction
- Le scanner thoracique à faible dose
- L’essai NLST
- Autres essais randomisés
- Perspectives
- **Thématiques de recherche**
- Conclusions

Lung Cancer 3

Prospects for population screening and diagnosis of lung cancer

John K Field, Matthijs Oudkerk, Jesper Holst Pedersen, Stephen W Duffy

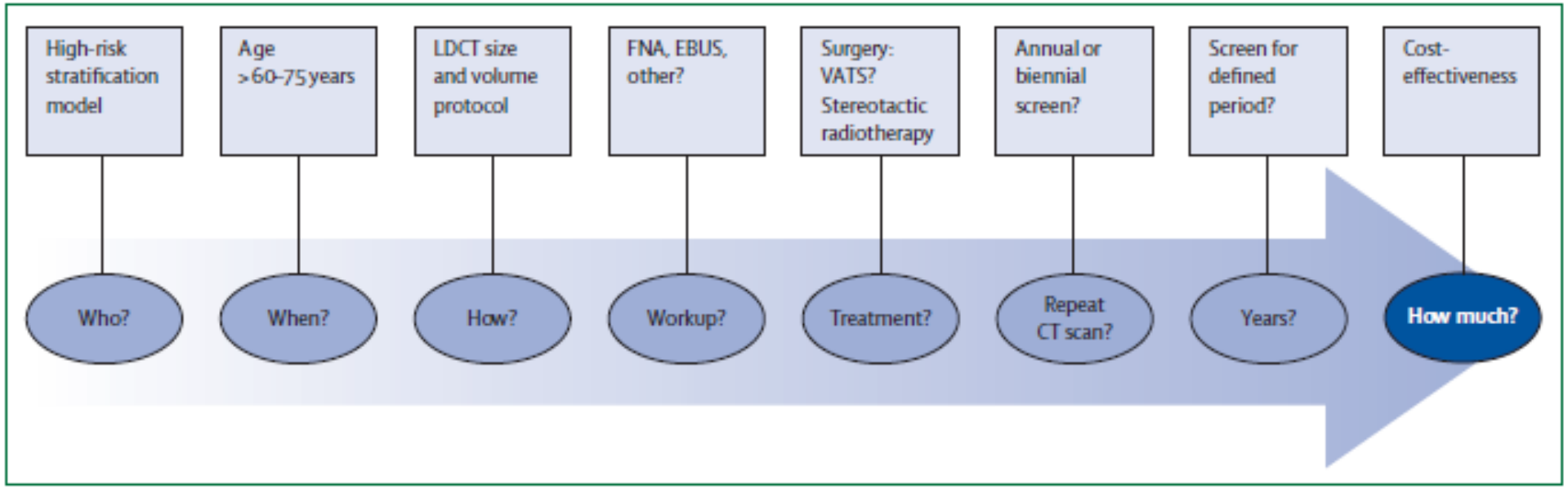


Figure 1: **Decisions for implementation of CT screening**
LDCT=low-dose CT. FNA=fine-needle aspiration. EBUS=endobronchial ultrasound. VATS=video-assisted thoracoscopic surgery.

Field JK et al Lancet 2013; 382-732-41

UZ LEUVEN

Thématiques de recherche

- **Définition de la population à haut risque**

  - **NLST:**
    Des personnes âgées de 50 à 75 ans, ayant fumé pendant au moins 30 paquêts-années, avec un tabagisme actif ou stoppé depuis moins de 10 ou 15 ans

  - **Liverpool Lung Project (LLP) Risk Model**
  - **USPS Task Force: étude comparative:**
    une population âgée de 55-80 ans, ayant fumé au moins 30 pâquets-années, fumeur actif ou stoppé depuis moins de 15 ans

  - **Quoi donc avec les non-fumeurs? Non-fumeuses?**
  - **Rôle pour les biomarqueurs et les marqueurs génétiques?**

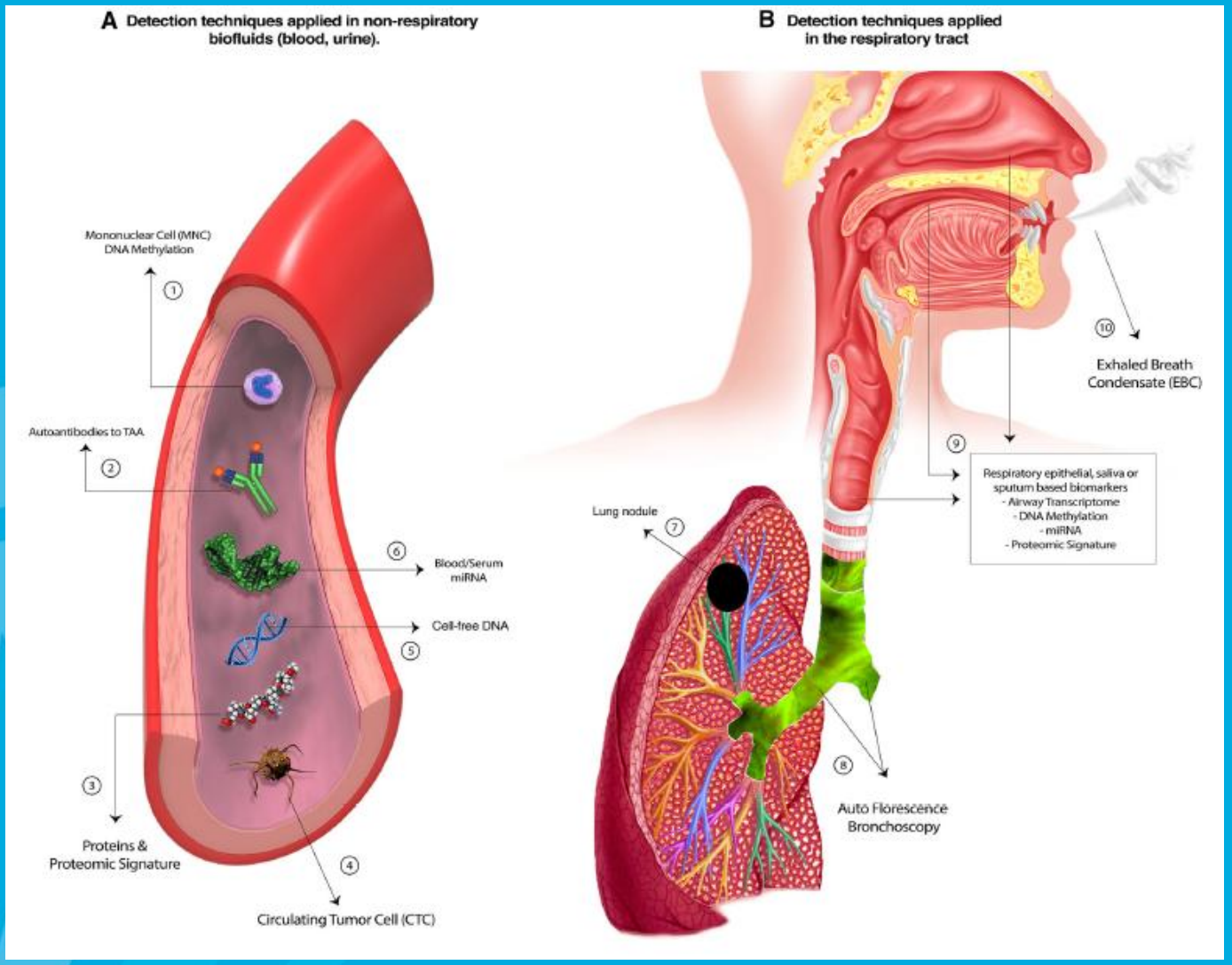
Benefits and Harms of Computed Tomography Lung Cancer Screening Strategies: A Comparative Modeling Study for the U.S. Preventive Services Task Force

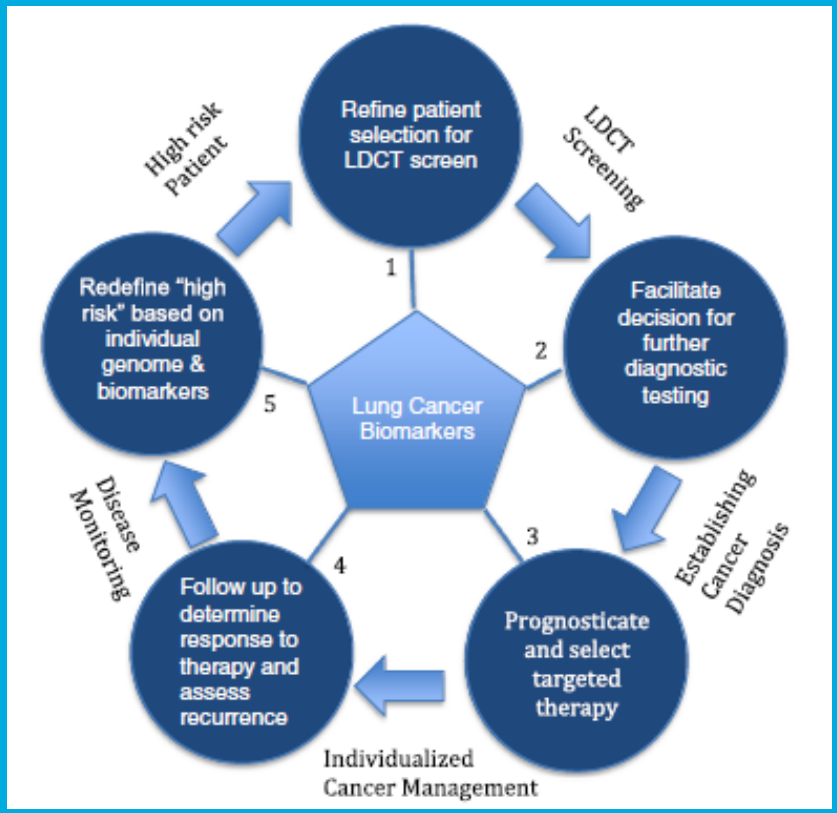
Harry J. de Koning, MD; Rafael Meza, PhD; Sylvia K. Plevritis, PhD; Kevin ten Haaf, MSc; Vidit N. Munshi, MS; Jihyoun Jeon, PhD; Saadet Ayca Erdogan, PhD; Chung Yin Kong, PhD; Summer S. Han, PhD; Joost van Rosmalen, PhD; Sung Eun Choi, SM; Paul F. Pinsky, PhD; Amy Berrington de Gonzalez, PhD; Christine D. Berg, MD; William C. Black, MD; Martin C. Tammemägi, PhD; William D. Hazelton, PhD; Eric J. Feuer, PhD*; and Pamela M. McMahon, PhD*

Raji OY et al Ann Intern Med 2012
De Koning H et al Ann Intern Med 2013 online 31-12-2013

Lung Cancer Screening Beyond Low-Dose Computed Tomography: The Role of Novel Biomarkers

Naveed Hasan · Rohit Kumar · Mani S. Kavuru





Hasan N et al Lung 2014

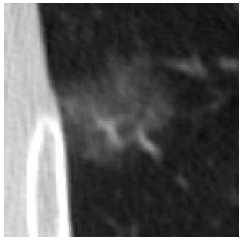
Thématiques de recherche

- **Standardisation des modalités techniques (des scanners)**
  - Scanner thoracique, multi-barrette, faible dose, épaisseur des coupes natives ≤ 1,25mm, controle d'exposition automatisée avec la technique de reconstruction itérative
  - Obtenir des images volumétriques des petits nodules
  - Risque d'irradiation minimale

- **Interprétation du scanner de dépistage**
  - Evaluation des nodules détectés: 2D, 3D
  - Lecture des images: (non-) radiologue, CAD software
  - Algorithme pour les nodules détectés: positifs, négatifs, intermediaires

Field JK et al Lancet Oncol 2013;14:e591
Prokop M Semin Respir Crit Care Med 2014;35:91
Kim MJ et al J Compt Assist Tomogr 2009;33:416

NELSON trial - *examination dose*



Weight	kVp	mGy	mSv
< 50 kg	80-90	0.8	< 0.4
50-80 kg	120	1.6	< 0.8
> 80 kg	140	3.2	< 1.6

Average dose: < 1 mSv

Potential cancers induced: < 1/50,000 scans

Future: individual adaptive exposure control

Xu DM et al Lung Cancer 2006;54:177

Thématiques de recherche

- **Prise en charge en cas de dépistage positif**
  - Examens complémentaires
  - Scanner tomographique (avec contraste iv)
  - Diagnostique histologique
  - PET scan (pour le bilan d'extension)
  - Traitement chirurgical (résection limitée?)

- **Prise en charge en cas de dépistage négatif**
  - Durée optimale du programme de dépistage (bi)annuel du cancer bronchique?
  - Cancers d'intervalle?

XU DM et al Lung Cancer 2006;54:177
Van't Westeinde SC et al Chest 2012;2:377
Van't Westeinde SC et al JTO 2011;6:1704
Field JK et al JTO 2013;9:141

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Thématiques de recherche

- Prise en charge du sevrage tabagique
- Risque induit par l'irradiation des scanners

Lung cancer screening and smoking abstinence: 2 year follow-up data from the Dutch–Belgian randomised controlled lung cancer screening trial

Carlijn Michelle van der Aalst,[1,2] Karien Anna Margaretha van den Bergh,[1] Marc Christiaan Willemsen,[3] Henricus Johannes de Koning,[1] Robertus Johannes van Klaveren[2]

Table 2 Smoking behaviour of male smokers in the screen and control arm after 2 years of follow-up

	Screen arm %*	N	Control arm %*	N	p Value
Median number of quit attempts (IQR)†	1 (2)	581	1(2)	503	0.47
Point prevalence of smoking abstinence‡	15.1	88/581	19.8	99/500	0.04
Prolonged smoking abstinence§	14.5	84/581	19.1	96/503	0.04
Continued smoking abstinence¶	13.9	81/581	18.7	94/503	0.03
Median duration of smoking cessation** (IQR) (months)	12.0 (17.0)	63	12.0 (15.5)	69	0.82

*Data are presented as a percentage unless indicated otherwise.
†Results are based on available data of respondents who were current smokers at follow-up (T1).
‡Point prevalence of smoking abstinence indicates that respondents did not smoke in the last 7 days.
§Prolonged smoking abstinence indicates that respondents have smoked <5 cigarettes since 2 weeks after the quit date.
¶Continued smoking abstinence indicates that respondents have smoked <5 cigarettes since the quit date.
**Results are based on available data of respondents who were former smokers at follow-up (T1).

van der Aalst CM et al Thorax 2010

Smoking habits in the randomised Danish Lung Cancer Screening Trial with low-dose CT: final results after a 5-year screening programme

Haseem Ashraf,[1,2] Zaigham Saghir,[1] Asger Dirksen,[1] Jesper Holst Pedersen,[3] Laura Hohwü Thomsen,[1] Martin Døssing,[4] Philip Tønnesen[1]

What is the key question?

Does screening for lung cancer with low-dose CT of thorax affect smoking behaviour?

What is the bottom line?

No significant difference was found in smoking behaviour during a 5-year period between the CT group versus the control group.

Why read on?

Overall, we found an increasing smoking cessation rate during this screening programme, higher motivation to quit at baseline predicted smoking abstinence at the final screening round.

Thorax online first 17 Jan 2014

Integration of Smoking Cessation into CT Screening Programs

- Lung cancer screening presents a new opportunity to reinforce smoking cessation in a setting of current smokers where a screening subject will frequently be involved in ongoing annual visits.
- With annual screening escalating approaches to tobacco cessation can be tested.

Action points:

- Stimulate further research in best practice for integration and personalization of cessation approach

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Le dépistage du cancer bronchique

- Introduction
- Le scanner thoracique à faible dose
- L’essai NLST
- Autres essais randomisés
- Perspectives
- Thématiques de recherche
- **Conclusions**

- LDCT Lung Cancer Screening: to be implemented?
- Recommendations from IASLC-SSAC awaited.
- Results of European LDCT screening trials pending.

- Ongoing Research:
  - Participant risk modeling
  - Radiological techniques, CAD, …
  - Smoking cessation
  - Cost-effectiveness of NLST, European trials (?).