# LDCT for Lung Cancer screening: Implications for a TB endemic region

DM SEMINAR

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March 8TH 2019

# Outline

- Lung cancer epidemiology
- Lung cancer screening methods and earlier trials
- LDCT trials – NLST and NELSON
- LDCT trials in tuberculosis endemic regions
- Pulmonary nodule evaluation in Asian population

# Lung Cancer Epidemiology

Worldwide – predicted in 2018

- Incidence - 2.1 million new cases
- Mortality - 1.8 million deaths

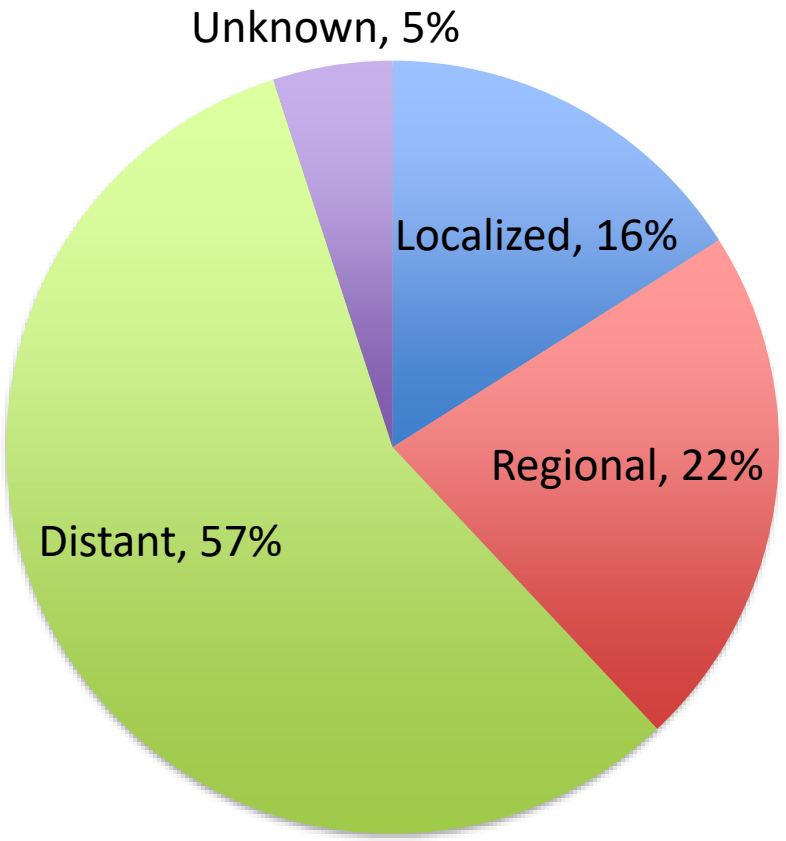
India – predicted in 2018

- Incidence - 67,795 new cases ($4^{th}$ MC cancer in India after breast, oral cavity and cervix)

- Mortality – 63,475 deaths ($3^{rd}$ MC cancer related deaths after breast and oral cavity)

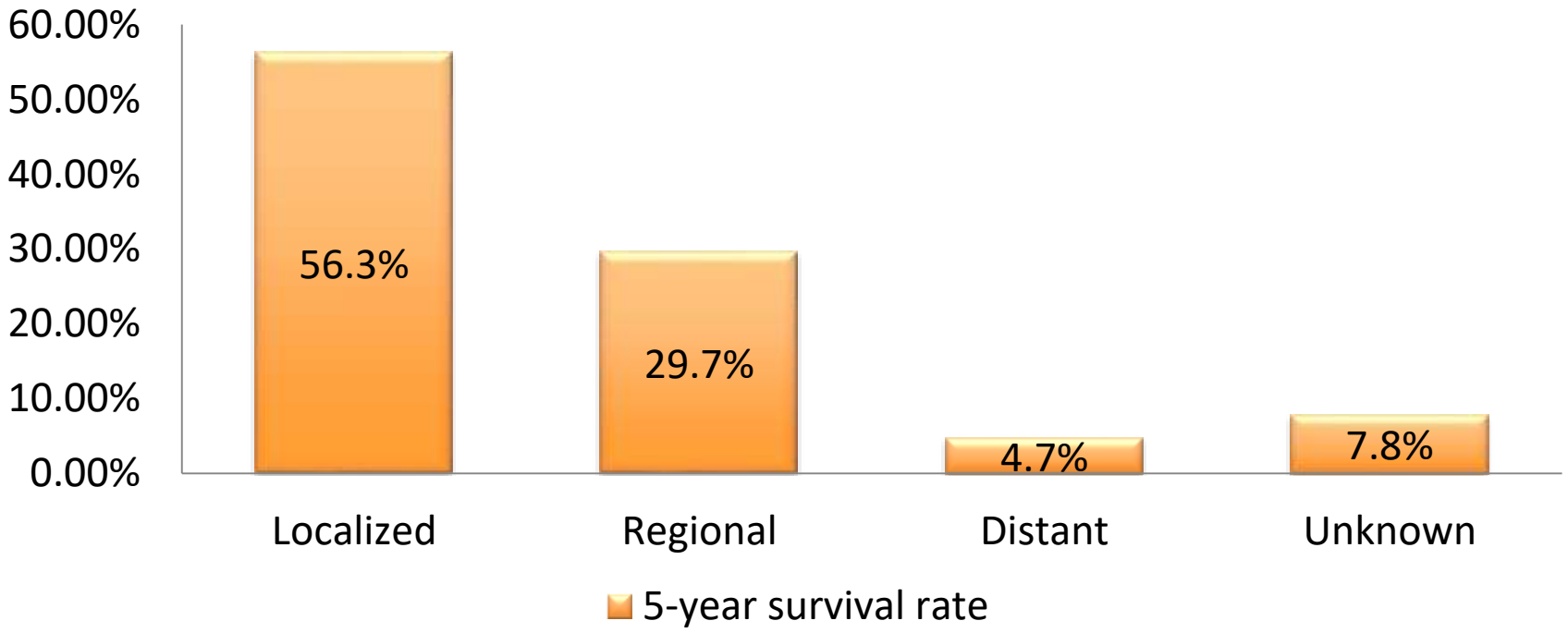
CA Cancer J Clin. 2018;68(6):394-424

# % of cases by stage at presentation




SEER Cancer Statistics Review, 1975-2015

# 5-Year Relative Survival




Percent surviving 5 years – 18.6%

SEER Cancer Statistics Review, 1975-2015

# Lung Cancer Screening - CXR

1951-1975: 10 prospective studies, of which 4 are RCTs –

- The Memorial-Sloan Kettering Lung Project (MSKLP) (sputum + CXR)
- The John Hopkins lung project (JHLP) (Sputum + CXR)
- The Mayo Lung project (MLP)
- The Czechoslovakian study (CS)

Cochrane Library

Cochrane Database of Systematic Reviews

# Screening for lung cancer (Review)

Manser R, Lethaby A, Irving LB, Stone C, Byrnes G, Abramson MJ, Campbell D

2013

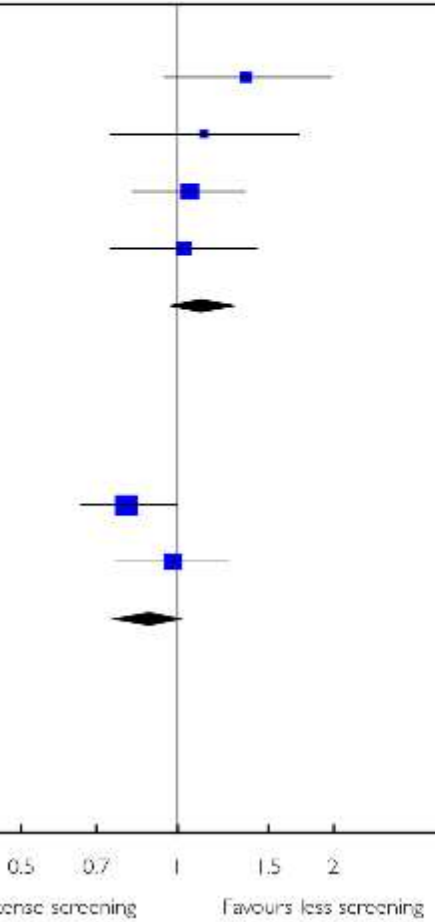
## Analysis 1.1. Comparison 1 Lung cancer screening with chest radiography +/- sputum cytology versus less intense screening, Outcome 1 Lung cancer mortality.

Review: Screening for lung cancer

Comparison: 1 Lung cancer screening with chest radiography +/- sputum cytology versus less intense screening

Outcome: 1 Lung cancer mortality

| Study or subgroup | More intense screening n/N | Less intense screening n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 More frequent chest x-ray screening versus less frequent screening | | | | | |
| Czech Study | 64/3171 | 47/3174 | | 17.0 % | 1.36 [ 0.94, 1.98 ] |
| Kaiser Foundation Study | 44/5156 | 42/5557 | | 14.6 % | 1.13 [ 0.74, 1.72 ] |
| Mayo Lung Project | 122/4618 | 115/4593 | | 41.8 % | 1.06 [ 0.82, 1.36 ] |
| North London Study | 82/29723 | 68/25311 | | 26.6 % | 1.03 [ 0.74, 1.42 ] |
| **Subtotal (95% CI)** | **42668** | **38635** | | **100.0 %** | **1.11 [ 0.95, 1.31 ]** |
| Total events: 312 (More intense screening), 272 (Less intense screening) | | | | | |
| Heterogeneity: $Chi^2$ = 1.55, df = 3 (P = 0.67); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 1.28 (P = 0.20) | | | | | |
| 2 Annual chest x-ray plus 4-monthly cytology versus annual x-ray alone | | | | | |
| Johns Hopkins Study | 141/5226 | 173/5161 | | 59.4 % | 0.80 [ 0.65, 1.00 ] |
| Mem Sloan-Kettering | 115/4968 | 120/5072 | | 40.6 % | 0.98 [ 0.76, 1.26 ] |
| **Subtotal (95% CI)** | **10194** | **10233** | | **100.0 %** | **0.88 [ 0.74, 1.03 ]** |
| Total events: 256 (More intense screening), 293 (Less intense screening) | | | | | |
| Heterogeneity: $Chi^2$ = 1.31, df = 1 (P = 0.25); $I^2$ =24% | | | | | |
| Test for overall effect: Z = 1.58 (P = 0.11) | | | | | |
| Test for subgroup differences: $Chi^2$ = 4.09, df = 1 (P = 0.04), $I^2$ =76% | | | | | |



## Analysis 2.1. Comparison 2 Annual chest x-ray screening versus usual care (no regular screening), Outcome 1 Lung cancer mortality at 6 years of follow up.

Review: Screening for lung cancer

Comparison: 2 Annual chest x-ray screening versus usual care (no regular screening)

Outcome: 1 Lung cancer mortality at 6 years of follow up

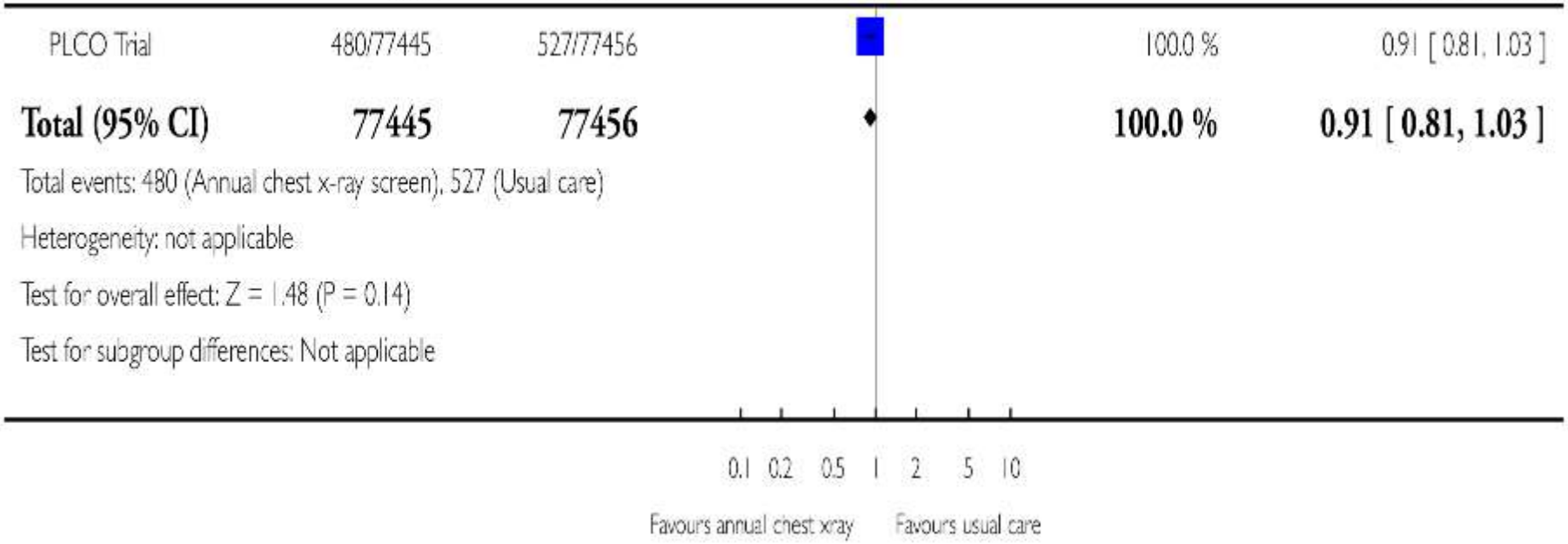
| Study or subgroup | Annual chest x-ray screen n/N | Usual care n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| PLCO Trial | 480/77445 | 527/77456 | | 100.0 % | 0.91 [ 0.81, 1.03 ] |
| **Total (95% CI)** | **77445** | **77456** | | **100.0 %** | **0.91 [ 0.81, 1.03 ]** |

Total events: 480 (Annual chest x-ray screen), 527 (Usual care)

Heterogeneity: not applicable

Test for overall effect: Z = 1.48 (P = 0.14)

Test for subgroup differences: Not applicable



Retrospective analysis –

When compared to spiral CT, CXR

- Median delay in diagnosis was found to be >1 year

The miss-rate for lesions

- ≤ 10mm was 70%
- 10-20mm was 30%
- 21-30mm was 25%

- The overall accuracy of interpretation for lung cancer – 61% for CXR, Sensitivity – 23%, Specificity – 96%, when compared to CT scan

Chest. 1999 Mar;115(3):720-4

# Low Dose CT scan

- Non contrast study
- Multi detector, helical CT scan
- High resolution image reconstruction
- Estimated effective dose – 1.4mSv
- 7-8mSv for CECT chest, 0.1mSv for CXR

AJR Am J Roentgenol. 2011;197(5):1165

# LDCT

| Study | Detectors | Voltage (kVp) | Tube current time product (mAs) | Pitch | Rotation time(s) | Effective dose (mSv) | Slice thickness (mm) | Reconstruction interval (mm) |
|---|---|---|---|---|---|---|---|---|
| I-ELCAP | ≥4 | ≤120 | ≤40 | 1.5 | 0.5 | 1-2 | 1.25 | 1.25 |
| NLST | ≥4 | 120-140 | 40-80 | 1.2-2.0 | - | 1.5 | 1.0-3.2 | 1.0-2.5 |
| NELSON | 16 | 80-140 | 20 | 1.5 | - | <2 | 1 | 0.7 |
| NCCN | ≥16 | 100-120 | ≤40 | - | ≤0.5 | 3-5 | ≤1 | - |
| K-LUCAS | 64 | 100-120 | 30-50 | 0.9-1.0 | 0.3-0.5 | 1.3 | 1.25 | 1-1.25 |

Cancer Imaging (2012) 12(3), 548-556

# National Lung Screening Trial

- Multicenter, RCT, USA
- 53,454 participants were enrolled between 2002 – 2004
- LDCT (26,722) vs CXR (26,732)
- 3 screenings – T0 (at randomization), T1 and T2 at 1-year intervals

Inclusion Criteria :

- 55 - 74 years of age at time of randomization
- Cigarette smoking of at least 30 pack years
- If former smokers - must have quit within the previous 15 years

N Engl J Med 2011;365:395-409.

# NLST

Positive test – "suspicious for" lung cancer

- Any non calcified nodule measuring at least 4 mm in any diameter
- Adenopathy
- Effusion

Minor abnormalities –

- Clinically significant conditions other than lung cancer
- After the third round of screening (T2), abnormalities suspicious for lung cancer that were stable across the three rounds

N Engl J Med 2011;365:395-409.

# 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) |

N Engl J Med 2011;365:395-409.

# 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) |

N Engl J Med 2011;365:395-409.

# NLST

Lung cancer specific mortality

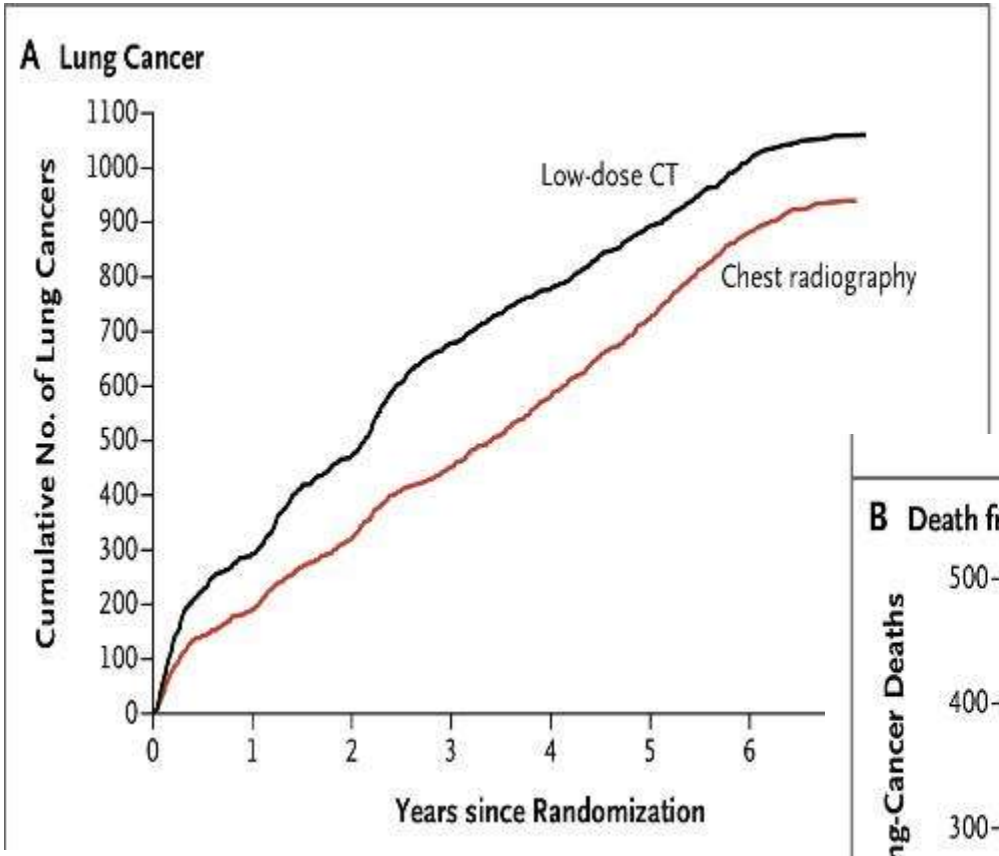
- 356 (LDCT) vs 443 (CXR) deaths from lung cancer
- 20.0% (95% CI, 6.8 to 26.7; P= 0.004) reduction in rate of death from lung cancer
- NNS – 320 individuals with high risk factors to prevent one death from lung cancer

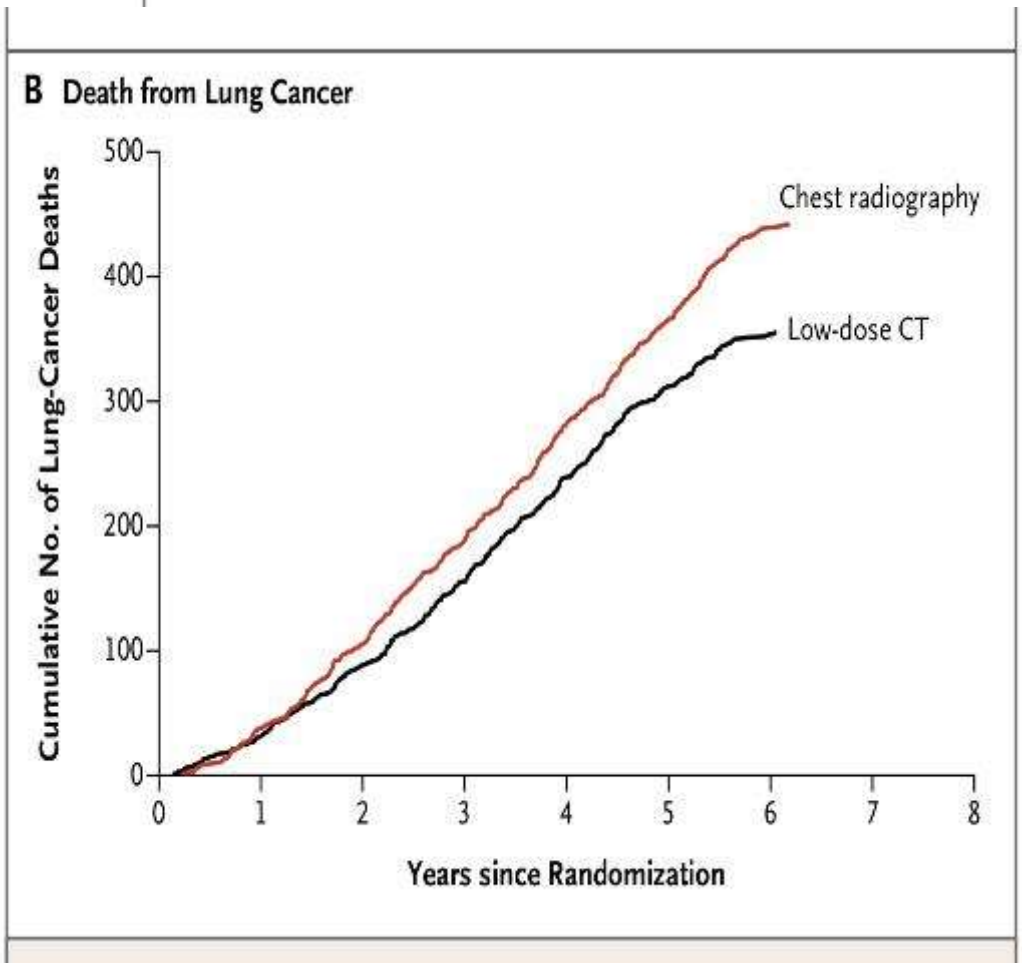
Overall mortality

- 1877 (LDCT) vs 2000 (CXR) deaths
- 6.7% reduction (95% CI, 1.2 to 13.6; P = 0.02) in the rate of death from any cause

N Engl J Med 2011;365:395-409.

# NLST




N Engl J Med 2011;365:395-409.

# NELSON trial
# Dutch-Belgian Randomized Lung Cancer Screening Trial

Hypothesis :

- Lung cancer screening by LDCT will reduce 10-year lung cancer mortality by 25% in high-risk (ex-)smokers between 50 and 75 years of age.

Inclusion Criteria :

- Men aged 50-75 years
- Smoked cigarettes - >15/day for >25 years or >10/day for >30 years

Cancer Imaging (2011) 11, S79-S84

# NELSON trial

*Table 1 Nodule categorization based on size and characteristics (new nodules) and growth rate (existing nodules) in NELSON study*

| Category | Definition | | |
|---|---|---|---|
| NODCAT 1 | A benign nodule (with fat/benign calcifications) or other benign abnormalities | | |
| NODCAT 2 | A nodule, smaller than NODCAT3, not belonging to NODCAT1 | | |
| | Solid | Partial solid | Non-solid |
| NODCAT 3 | $50 \leq V \leq 500\,mm^3$ | Solid component: $50 \leq V \leq 500\,mm^3$ | $d_{mean} \geq 8\,mm$ |
| | Pleural based: $5 \leq d_{min} \leq 10\,mm$ | Non-solid component: $d_{mean} \geq 8\,mm$ | |
| NODCAT 4 | $V > 500\,mm^3$ Pleural based: $d_{min} > 10\,mm$ | Solid component: $V > 500\,mm^3$ | Non-existent category |
| GROWCAT A | VDT > 600 days | | |
| GROWCAT B | $400 \leq VDT \leq 600$ days | | |
| GROWCAT C | VDT < 400 days, or new solid component in non-solid lesion | | |

$V$, volume; $d_{min}$, minimal diameter; $d_{mean}$, mean diameter; VDT, volume-doubling time.

Cancer Imaging (2011) 11, S79S84

# NELSON trial

- Management was determined based on the highest nodule category found
- NODCAT 3 - indeterminate test result which required a repeat scan 3-4 months later to assess growth
- Growth was defined as change in volume of at least 25% between scans

Cancer Imaging (2011) 11, S79S84

# NELSON trial

- LDCT screening at baseline (round 1), after 1 year (round 2), after 3 years (round 3) and after 5.5 years after baseline (round 4)

- 15,822 participants randomized in 1:1 ratio to screening LDCT (7915) vs no screening (7909)

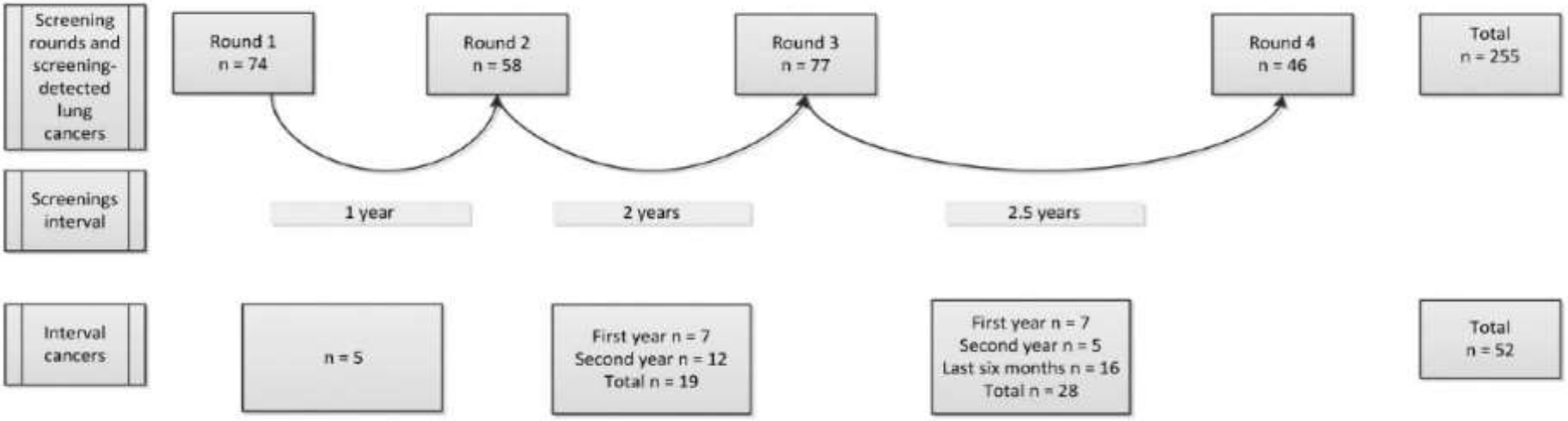
Thorax 2017;72:48–56.

# NELSON

**Table 5** Screening test performance across the four screening rounds

| | R1* | 95% CI | R2* | 95% CI | R3* | 95% CI | R4 | 95% CI |
|---|---|---|---|---|---|---|---|---|
| Lung cancer detection rate, % | 0.9 | 0.7 to 1.2 | 0.8 | 0.6 to 1.0 | 1.1 | 0.8 to 1.3 | 0.8 | 0.6 to 1.1 |
| Positive predicted value, % | 35.5 | 28.4 to 42.1 | 42.0 | 34.4 to 49.6 | 45.5 | 37.6 to 53.5 | 41.0 | 31.6 to 50.5 |
| False-positive (FP) rate after positive screening, % | 64.5 | 57.9 to 71.6 | 58.0 | 50.4 to 65.6 | 54.5 | 46.7 to 62.4 | 59.0 | 49.5 to 68.4 |
| Ratio TP/FP[2] | 0.69 | – | 0.72 | – | 0.83 | – | 0.69 | – |
| Overall FP rate† | – | – | – | – | – | – | 1.2[2] | – |
| Number needed to screen to detect 1 lung cancer | 108 | – | 133 | – | 92 | – | 123 | – |

*Screening test performances across the first three rounds.[12]
†This is the overall FP rate of the NELSON trial across all four screening rounds.
TP, true positive.




Thorax 2017;72:48–56.

| Factors | NLST | NELSON |
|---|---|---|
| Screening design | LDCT vs CXR | LDCT vs no screening |
| Screening rounds | 3 | 4 |
| Length of screening interval (years) | 1 | 1, 2 and 2.5 |
| Year of initiation | 2002 | 2003 |
| Enrolled participants | 53,454 | 15,822 |
| Positive result | Maximum axial diameter ≥4mm | Volume >500mm$^3$ or Volume 50-500mm$^3$ and VDT < 400 days |
| Negative result | Maximal axial diameter <4 mm | Volume <50mm$^3$ |
| Entry criteria | | |
| Age (yrs) | 55-75 | 50-75 |
| Smoking status | Current and former smokers | Current and former smokers |
| Smoking cessation | <15 years | <10 years |
| Smoking history | ≥30 pack years | ≥15 per day for 25 years or ≥10 per day for 30 years |

J. Compar. E ffect. Res. (2013) 2(5)

| Cumulative data | NLST | NELSON |
|---|---|---|
| Positive screening result | 24.2% | 1.9% |
| False positive rate after positive screening result | 96.4% | 59.4% |
| Lung cancer detection rate | 2.4% | 3.2% |
| % of Stage I cancers detected | 61.6% | 69.4% |
| LDCT sensitivity for LC | 93.8% | 94.6% |
| LDCT specificity for LC | 73.4% | 98.3% |

J. Compar. Effect. Res. (2013) 2(5)

Thorax 2017;72:48–56.

- 26% reduction in lung cancer deaths at 10 years of study follow-up

(NELSON trial results were presented at WCLC 2018, however the results were not published yet)

- Difference in inspiration level – difference in nodule rotation – variable diameter measurements (NLST)

- Volume of the nodule stays constant (NELSON)

## TABLE 3. OVERVIEW OF CANCER STAGE AT DIAGNOSIS OF COMPUTED TOMOGRAPHY (CT)–DETECTED LUNG CANCERS IN RANDOMIZED CT SCREENING TRIALS

| Trial (Ref.) | Participants in Screening Arm (*n*) | Screening Rounds (*n*) | Length of Screening Interval (*yr*) | Males to Females (%:%) | No. of Published CT-Detected Lung Cancers | Stage IA + IB Lung Cancers [*n* (%)] | Stage IIIB + IV Lung Cancers [*n* (%)] |
|---|---|---|---|---|---|---|---|
| NLST (8) | 26,722 | 3 | 1 | 59.0:41.0 | 649 | 400 (61.6) | 130 (20.0) |
| NELSON | 7,915 | 4 | 1, 2, and 2.5 | 83.5:16.5 | 209 | 148 (70.8) | 17 (8.1) |
| DLST (36) | 2,052 | 5 | 1 | 54.6:45.4 | 69 | 47 (68.1)* | 11 (15.9)† |
| ITALUNG (7) | 1,613 | 4 | 1 | 64.2:35.8 | 22 | 11 (50.0)‡ | 5 (22.7) |
| DANTE (37) | 1,276 | 4 | 1 | 100.0:0.0 | 58 | 41 (70.7) | 4 (6.9) |
| MILD (38) | 1,190 | 10 | 1 | 68.4:31.6 | 29 | 18 (62.1) | 4 (20.0) |
| | 1,186 | 5 | 2 | 68.5:31.5 | 20 | 14 (70.0) | 5 (17.2) |
| LUSI (39) | 2,029 | 4 | 1 | 64.8:35.2 | 22 | 18 (81.8) | 0 (0) |
| Total | 43,983 | 3 to 10 | 1 to 2.5 | 65.4:34.6 | 1,078 | 697 (64.7)§ | 118 (10.9)* |

*Definition of abbreviations*: CT = computed tomography; DLST = Danish Lung Cancer Screening Trial; MILD = Multicentric Italian Lung Detection; NELSON = Nederlands Leuvens Longkanker Screenings Onderzoek (Dutch–Belgian Lung Cancer Screening Trial); NSLT = National Lung Screening Trial.

* This does not include two participants diagnosed with limited-stage small cell lung carcinoma.

† This includes the participant diagnosed with extensive-stage small cell lung carcinoma.

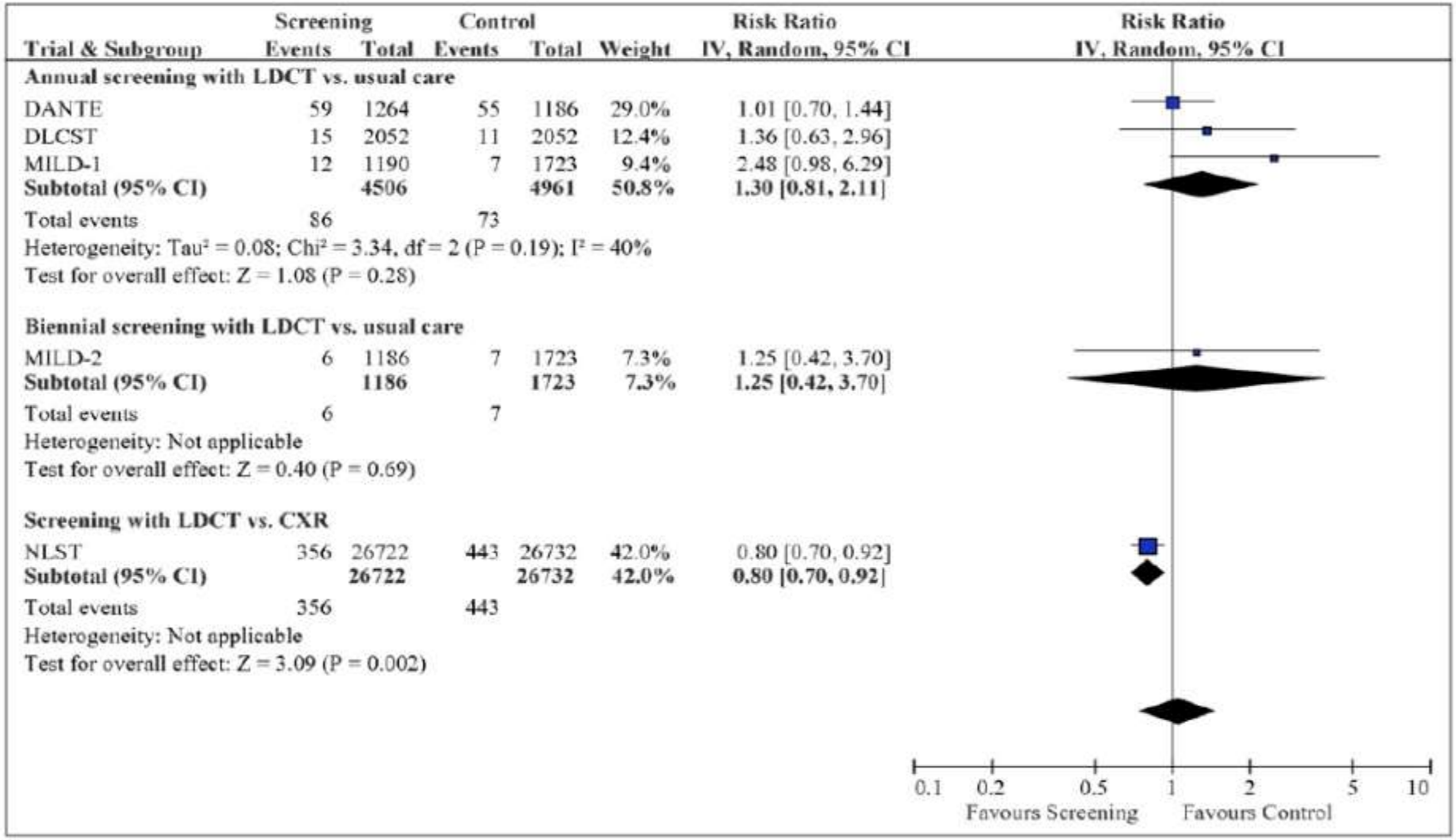
‡ This does not include the three participants diagnosed with limited-stage small cell lung carcinoma.

§ This does not include the four participants with limited-stage small cell lung carcinoma.

Am J Respir Crit Care Med Vol 187, Iss. 8, pp 848–854, Apr 15, 2013

| TRIAL | Participants undergoing LDCT | Positivity rate after baseline | Biopsies | Lung cancer detected |
|---|---|---|---|---|
| NLST | 26,722 | 27% | 2.8% | 2.4% |
| ELCAP | 1000 | 23% | 2.8% | 2.7% |
| DLCST | 2052 | 29% | 1.2% | 0.8% |
| DANTE | 1276 | 15% | 4.1% | 2.2% |
| NELSON | 7582 | 6.5% | NR | 3.2% |

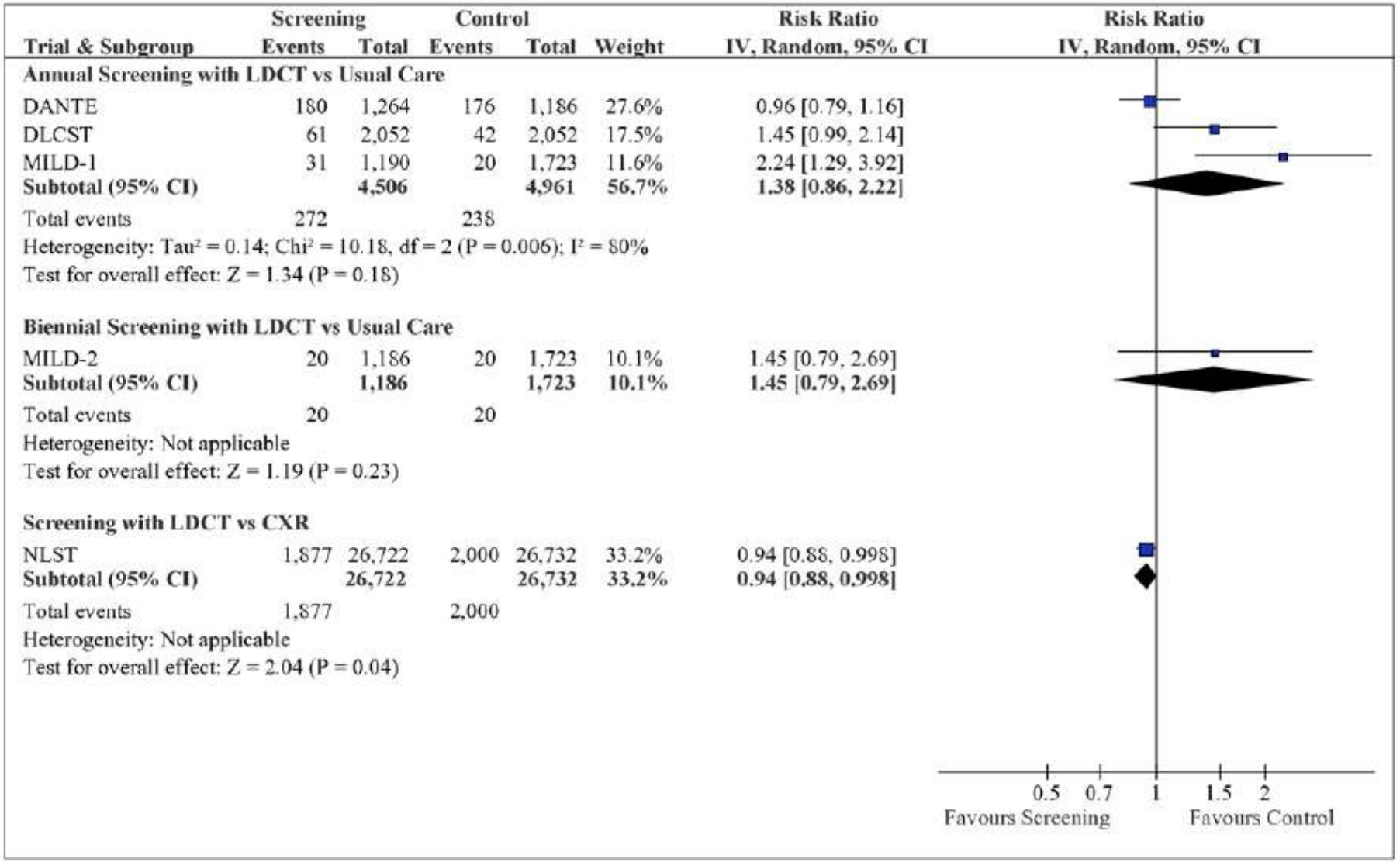
Ann Thorac Surg 2016;101:481–8




MILD-1 = uses data from intervention arm that received annual LDCT screening; MILD-2 = uses data from intervention arm that received biennial LDCT screening

**Fig. 2.** Forest plot for effect of LDCT screening on lung cancer mortality.

Preventive Medicine 89 (2016) 301–314




MILD-1 = uses data from intervention arm that received annual LDCT screening; MILD-2 = uses data from intervention arm that received biennial LDCT screening

**Fig. 3.** Forest plot for effect of LDCT screening on all-cause mortality.

Preventive Medicine 89 (2016) 301–314

# Other benefits of LC screening

Improved QOL

- Reduction in disease related morbidity
- Reduction in treatment related morbidity
- Reduction in anxiety(?) and psychosocial burden
- Increased smoking cessation rates (?)

# Other benefits of LC screening

Incidental findings

- 7.9% of participants in LDCT arm of NLST
- 37 of 1276 men screened in DANTE trial

- MC were – Emphysema and coronary artery calcification

- Mediastinal mass, LN enlargement, aortic aneurysm, renal mass etc.

# Risks of LC screening

False positive results

- Range from 10-43%
- Cumulative risk is 33% for a person undergoing LC screening with 2 sequential annual scans
- Benign intrapulmonary LN and non calcified granulomas

# Risks of LC screening

- Volumetric analysis in NELSON trial – decreases the false positives

Lung-RADS (Lung Imaging Reporting and Data System)

- Increased size threshold from 4 mm greatest transverse diameter to 6 mm transverse bi-dimensional average

- 20 mm for nonsolid nodules

- Growth for preexisting nodules (>1.5 mm)

| Category Name | No : | Findings | Management | Probability of malignancy |
|---|---|---|---|---|
| Negative | 1 | No nodules<br>Nodules with complete/central/popcorn calcification<br>Fat containing nodules | Annual LDCT | <1% |
| Benign | 2 | SN: <6 mm, New - <4 mm | Annual LDCT | <1% |
| | | PSN: <6 mm in baseline | | |
| | | NSN: <20 mm or<br>≥20 mm and unchanged | | |
| Probably benign | 3 | SN: ≥6 to <8 mm at baseline or<br>New – 4 mm to <6 mm | 6 month LDCT | 1-2% |
| | | PSN: ≥6 mm with solid component <6mm or<br>New <6 mm | | |
| | | NSN: ≥20 mm on baseline CT or new | | |
| Suspicious | 4A | SN: ≥8 to <15 mm at baseline or<br>Growing < 8 mm or<br>New 6 to <8 mm<br>PSN: ≥6 mm with solid component ≥6 mm to <8 mm or<br>new or growing <4 mm solid component<br>Endobronchial nodule | 3 month LDCT; PET/CT may be used when there is a ≥8mm solid component | 5-15% |
| | 4B | SN: ≥15 mm or<br>New or growing, and ≥8 mm<br>PSN: a solid component ≥8 mm or<br>New or growing ≥4 mm solid component | CECT Chest ± PET/CT and tissue sampling. PET/CT may be used when there is a ≥8mm solid | >15% |
| | 4X | Category 3 or 4 nodules with additional findings that increase the suspicion of malignancy | | |

# Application of Lung-RADS to NLST

| | Lung-RADS at baseline | NLST at baseline | Lung-RADS after baseline | NLST after baseline |
|---|---|---|---|---|
| Sensitivity | 84.9% | 93.5% | 78.6% | 93.8% |
| False positive result rate | **12.8%** | 27.3% | **5.3%** | 21.8% |
| PPV | 6.9% | 3.8% | 11.0% | 3.5% |
| NPV | 99.81% | 99.9% | 99.81% | 99.93% |

Ann Intern Med. 2015;162:485-491

# Risks of LC screening

| Trial | False positive rate | Proportion undergoing invasive procedure | Major complication associated with surgical procedure |
|---|---|---|---|
| NLST | 96.4% | 24% | 12% |
| NELSON | 1.2% | 23% | 10.7% |
| DANTE | 22.9% | 22% | 29% |
| DLCST | 7.9% | 16.6% | 38% |
| MILD | 0.8% | 6.4% | NR |
| UKLS | 3.6% | 10.3% | NR |

Br J Radiol;91:20170460

# BRELT1: First Brazilian LC screening Trial

- Single center study
- Jan 2013 to July 2014
- Inclusion criteria similar to NLST
- 790 participants were enrolled
- Positive scans – indeterminate pulmonary nodules >4 mm (similar to NLST)

Ann Thorac Surg 2016;101:481–8

# BRELT1 Protocol

*Table 1. Decision Protocol for the First LDCT Round*

| Size | Solid Nodules |
|---|---|
| >4 mm and ≤6 mm | Follow-up LDCT in 6 mo |
| >6 mm and ≤8 mm | Follow-up LDCT in 3 mo |
| >8 mm | Calculate pretest probability:<br>Low (<6%): follow-up LDCT in 3 or 6 mo<br>Intermediate (6%–60%): PET/CT<br>High (>60%): biopsy or surgical resection |
| | **GGO or Partially Solid Node** |
| Pure GGO ≤5 mm | Annual follow-up |
| Pure GGO >5 mm | Follow-up LDCT in 3 mo |
| Partially solid node | Follow-up LDCT in 3 mo |

GGO = ground-glass opacity; LDCT = low-dose computed tomography; PET/CT = positron emission tomography/computed tomography.

# BRELT1 Results

*Table 2. Distribution According to the Major Nodule's Size, Lung Cancer Prevalence and Approach Based on 312 Positive Studies in 790 Participants*

| Nodule Size | n (%) | LDCT (3–6 mo) | PET/CT | Biopsy | Lung Cancer |
|---|---|---|---|---|---|
| 4 to <6 mm | 167 (21.1) | 166 | 1 | 1[a] | . . . |
| 6 to <8 mm | 72 (9.1) | 70 | 2 | 2 | 2 |
| 8 to <10 mm | 28 (3.6) | 21 | 5 | 2 | 1 |
| 10 to <20 mm | 39 (4.9) | 20 | 11 | 13 | 5 |
| 20 to <30 mm | 4 (0.5) | 1[b] | . . . | 2 | 1 |
| >30 mm | 2 (0.3) | . . . | . . . | 2[c] | 1 |
| Mediastinal/other | 3 (0.4)[d] | . . . | . . . | 3 | . . . |
| Total | 312/790 (39.5) | 278/312 (89.1%) | 19/312 (6.1%) | 25/312 (8%) | 10/312 (3.2) |

[a] Endobronchial nodule. [b] Nodule with benign calcifications (scar tissue)—stable after 1-y follow-up. [c] Stage IV disease diagnosed with abdominal metastatic disease/cavitated lesion (tuberculosis). [d] Mediastinal lesions (not counted as lung nodules).

LDCT = low-dose computed tomography; PET/CT = positron emission tomography/computed tomography.

| TRIAL | Participants undergoing LDCT | Positivity rate after baseline | Biopsies | Lung cancer |
|---|---|---|---|---|
| NLST | 26,722 | 27% | 2.8% | 1.0% |
| ELCAP | 1000 | 23% | 2.8% | 2.7% |
| DLCST | 2052 | 29% | 1.2% | 0.8% |
| DANTE | 1276 | 15% | 4.1% | 2.2% |
| NELSON | 7582 | 6.5% | NR | 2.6% |
| **BRELT1** | **790** | **39.5%** | **3.1%** | **1.3%** |

# China

- Multicenter, RCT, 1:1 randomization
- LDCT (3512) vs standard care (3145)
- Nov 2013 to Nov 2014

Inclusion criteria :

- Age - 45-70 years and at least one risk factor
- ≥20 pack year history
- H/o any cancer in close family members
- Prior h/o any cancer in the participant
- Occupational exposure to carcinogens
- Long h/o passive smoking (>2 hr every day for at least 10 years)
- Long term exposure to cooking oil fumes

Lung Cancer 117 (2018) 20–26

Frequency of positive screening results.

| Features | Cases (%) | Lung cancers confirmed (%) | Adenocarcinomas in situ | Benign lesions confirmed* (%) | Metastases from other cancer (%) | Benign lesions considered* (%) | Under observation (%) |
|---|---|---|---|---|---|---|---|
| Overall | 804(22.9%) | 51 (1.5%) | 4 (0.1%) | 5 (0.1%) | 1 (0.03%) | 37 (1.1%) | 706 (20.1%) |
| Size of nodules | | | | | | | |
| < 5 mm | 325 (9.3%) | | | | | | 325 (9.3%) |
| ≥5–6 mm | 338 (9.6%) | | | | | | 338 (9.6%) |
| > 6–10 mm | 74 (2.1%) | 18 (0.5%) | 2 (0.06%) | 4 (0.1%) | | 20 (0.6%) | 30 (0.9%) |
| > 10–20 mm | 45 (1.3%) | 23 (0.7%) | 1 (0.03%) | | 1 (0.03%) | 11 (0.3%) | 9 (0.3%) |
| > 20–30 mm | 18 (0.5%) | 8 (0.2%) | 1 (0.03%) | 1 (0.03%) | | 5 (0.1%) | 3 (0.09%) |
| > 30 mm | 4 (0.1%) | 2 (0.06%) | | | | 1 (0.03%) | 1 (0.03%) |

- Positive results – 22.9% (804/3512)
- Lung cancer detection rate was 1.5% (51/3512)
- False positive rate – 21.8% (753/3461)

Further analysis, on increasing the nodule size threshold from 4mm to

- 5 mm – 13.6%
- 6 mm – 6.9%
- 7 mm – 4.0%
- 8 mm – 3.2% - positive screen rate

# Taiwan

- Single center, observational study
- Jan 2012 to Dec 2012

Inclusion Criteria –

- Asymptomatic adults aged ≥18 years
- No prior h/o any cancer
- Self referral basis
- Smoking h/o not necessary

Positive scan : any non calcified nodule ≥4 mm in diameter

J Formos Med Assoc (2016) 115, 163-170

- 3339 participants were enrolled
- 38.3% had positive baseline results
- 34 lung cancers were detected (1.02%)

- 6.2% (8 of 129) of LC detected are in those aged younger than 50 years with a positive family history of first-degree relatives having cancers
- Around 50% of participants were non smokers

- Asian population may need a different eligibility criteria for LC screening

# South Korea

- August 1999 – Sept 2003
- Single center, observational study
- Age ≥45 years and either ≥20 pack years (high risk group) or <20 pack year smoking or non smokers (low risk group)
- 6406 participants underwent LDCT

J Korean Med Sci 2005; 20: 402-8

- For solid nodule and >10 mm – immediate intervention (tissue diagnosis) was done
- For solid nodule <10 mm – follow up scan 6 months later
- For GGO >10 mm - immediate intervention (tissue diagnosis) was done
- For GGO <10 mm – f/u scan after 2 months, then after 6 months and annually thereafter

- 35% (2,255 of 6,406) of screened subjects had at least one or more non-calcified nodules (n=4,037)

- 2,085 subjects had 3,783 solid nodules (mean- 1.8 nodules per subject)

- 170 subjects had 254 GGO nodules (mean- 1.5 nodules per subject)

23 lung cancers were detected with an overall detection rate of

- 0.36% (23 of 6,406)
- 0.57% (23 of 4,037) of non calcified nodules

**Table 1.** Characteristics of non-calcified nodules detected by low-dose screening CT

| Group | Solid | | | | GGO | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | <5 mm | 5-10 mm | >10 mm | Total | <5 mm | 5-10 mm | >10 mm | Total | |
| High risk | 1,887 (950) | 191 (144) | 28 (26) | 2,106 (1120) | 46 (21) | 65 (50) | 26 (23) | 137 (94) | 2,243 (1,214) |
| Low risk | 1,479 (816) | 174 (125) | 24 (24) | 1,677 (965) | 52 (24) | 53 (40) | 12 (12) | 117 (76) | 1,794 (1,041) |
| Total | 3,366 (1,766) | 365 (269) | 52 (50) | 3,783 [1.81] (2,085) | 98 (45) | 118 (90) | 38 (35) | 254 [1.49] (170) | 4,037 [1.79] (2,255) |

Numbers in parenthesis are number of subjects and numbers in bracket are number of nodules per person. GGO, ground-glass opacity.

# K-LUCAS – pilot project
# Korean LC screening

- 2015 – Korean multi-society collaborative committee recommended guidelines for LC screening
- K-LUCAS – pilot study to evaluate the feasibility of LC screening protocol using LDCT and Lung-RADS
- Inclusion criteria - similar to NLST
- Only radiological results of the pilot study were reported
- 256 participants underwent LDCT

Korean J Radiol 19(4), Jul/Aug 2018

**Table 4. Distribution of Nodules Detected on LDCT Screening in Our Pilot Study for K-LUCAS Project**

| Characteristics | Values, n (%) |
|---|---|
| No nodule | 126 (49.2) |
| Any noncalcified nodule | 121 (47.3) |
| Any noncalcified nodule ≥ 4 mm | 74 (28.9) |
| Solid nodules only | 65 (87.8) |
| Subsolid nodules only | 5 (6.8) |
| Both solid and subsolid nodules | 4 (5.4) |

**Table 5. American College of Radiology Lung-RADS Categories Based on Initial Findings of LDCT in Our Pilot Study for K-LUCAS Project**

| Lung-RADS Category | Values, n (%) |
|---|---|
| 1 | 146 (57.1) |
| 2 | 91 (35.5) |
| 3 | 10 (3.9) |
| 4 | 9 (3.5) |
| A | 8 |
| B | 1 |
| X | 0 |
| Lung-RADS screening results | |
| Negative (category 1 and 2) | 237 (92.6) |
| Positive (category 3 and 4) | 19 (7.4) |

Lung-RADS = Lung Imaging Reporting and Data System

- One patient had lung cancer after baseline scan (0.4%)

- Application of Lung-RADS significantly decreases the false-positivity rate where tuberculosis is endemic

# Asian population

- Average age of onset of lung cancer is much earlier (40-50yrs)
- Most of them - non smokers
- Exposure to endemic risk factors (air pollution, volatile cooking oils and tuberculosis)
- Resource limitations, cultural and religious beliefs

- Applying NLST criteria to Asian population – 91.6% lung cancer cases would have missed (retrospective analysis)

- Female sex and family history of any cancer – appear to be stronger predictors

- Application of American risk calculators – do not factor in areas of high TB prevalence

- Nodule is whether tuberculosis or lung cancer ?

- Both of them need an aggressive approach for management

In a moderate risk patient :

- Less emphasis on PET
- More emphasis on use of non surgical biopsy procedures for definitive diagnosis

# PET/CT

- Retrospective study from India
- 191 patients with solitary pulmonary nodule undergoing FDG-PET/CT
- The final pathological diagnosis was malignancy in 75.3% (144/191) of nodules

Indian J Cancer 2017;54:271-5.

**Table 1: Number and pathology of malignant and benign pulmonary nodules**

| Pathology | *n* |
|---|---|
| Malignant | 144 |
| Adenocarcinoma | 84 |
| Squamous cell carcinoma | 30 |
| Adenocarcinoma *in situ* (BAC) | 05 |
| Low-grade neuroendocrine carcinoma | 22 |
| Small cell carcinoma | 01 |
| PNET | 01 |
| Malignant spindle cell tumor | 01 |
| Benign | 47 |
| Tuberculosis | 16 |
| Nonspecific inflammations | 24 |
| Fungal | 02 |
| Sclerosing hemangiomas | 02 |
| Chondroid hamartomas | 02 |
| Solitary fibrous tumor | 01 |
| Total | 191 |

## Table 2: Median and range of maximum standardized uptake value of malignant nodules

| Pathology | Median $SUV_{max}$ (range) |
|---|---|
| Adenocarcinoma and squamous cell carcinoma | 11.2 (3.3-34.6) |
| Adenocarcinoma *in situ* (BAC) | 4.3 (4.2-9.7) |
| Low grade neuroendocrine carcinoma (carcinoid) | 3.8 (0-20.6) |
| Small cell carcinoma | 5.5 (5.5) |
| PNET | 10.8 (10.8) |
| Malignant spindle cell tumor | 10.9 (10.9) |

$SUV_{max}$=Maximum standardized uptake values; BAC=Bronchioloalveolar carcinoma; PNET=Pancreatic neuroendocrine tumor

## Table 3: Median and range of maximum standardized uptake value of benign nodules

| Pathology | Median $SUV_{max}$ (range) |
|---|---|
| Tuberculosis | 10.3 (2.7–22.5) |
| Nonspecific inflammations | 3.5 (0–21.2) |
| Fungal | 2.5 (1.5–3.5) |
| Sclerosing hemangioma | 5.5 (4.0–7.0) |
| Chondroid hamartoma | 1.0 (0–2.1) |
| Solitary fibrous tumor | 0 (0) |

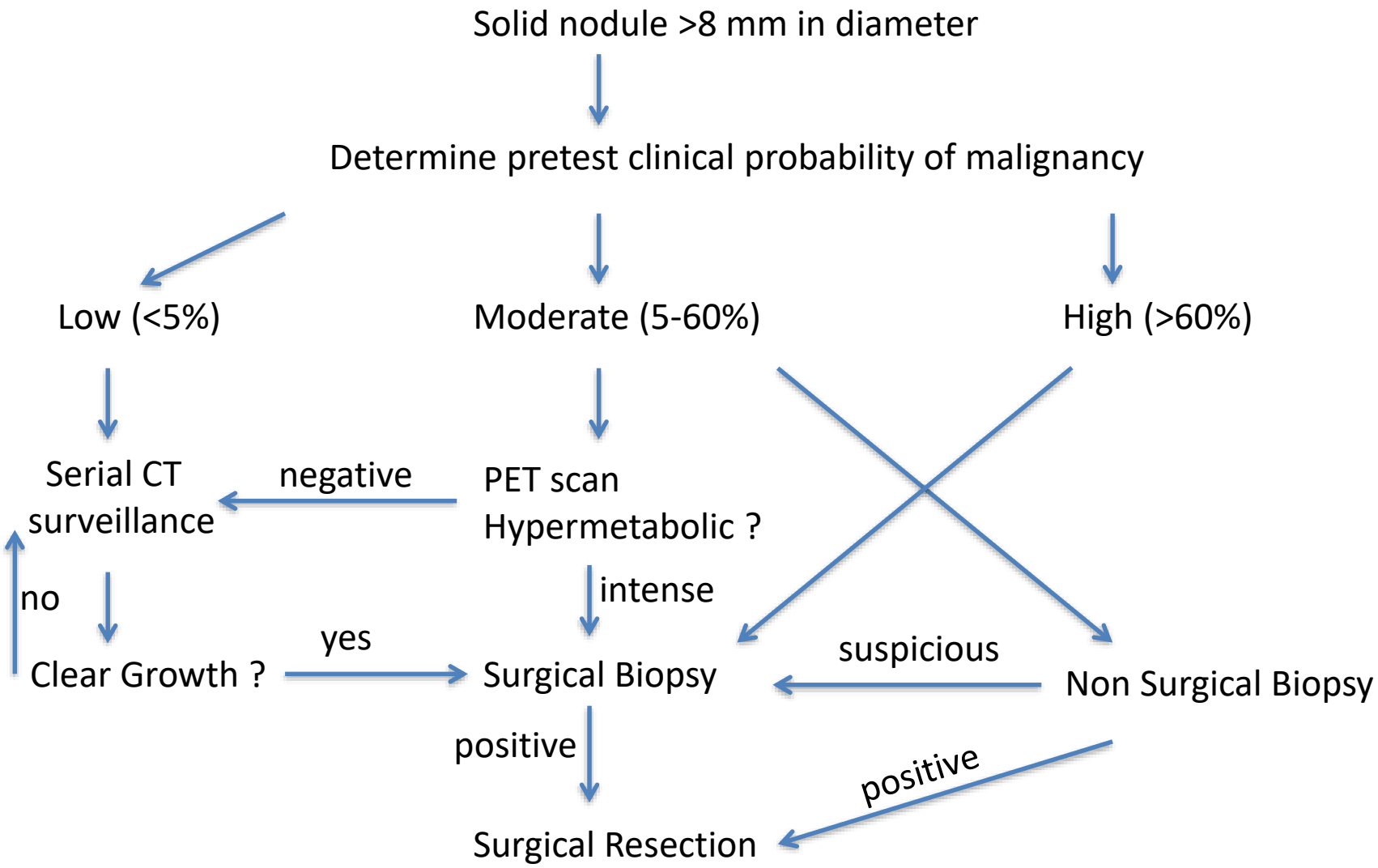
$SUV_{max}$=Maximum standardized uptake values

**Table 4: Causes of false positive and false negative positron emission tomography studies based on standardised uptake value cut-off - 2.5**

| Pathology | *N* | Median $SUV_{max}$ (range) |
|---|---|---|
| False positive ($SUV_{max}$ >2.5) | | |
| Tuberculosis | 16 | 10.3 (2.7–22.5) |
| Nonspecific inflammations | 11 | 4.6 (2.7–21.2) |
| Fungal granuloma | 01 | 3.5 (3.5) |
| Sclerosing hemangioma | 02 | 5.5 (4.0–7.0) |
| Total | 30 | |
| False negative ($SUV_{max}$ <2.5) | | |
| Low grade neuroendocrine carcinoma (carcinoid) | 08 | 2.0 (0–2.4) |

- 24.7% (47/191) were benign
- 64% (30/47) had a false positive PET-CT at a SUV cut-off of 2.5

# CHEST recommendations for SN - Asia




CHEST 2016; 150(4):877-893

- The expert panel recommends that regardless of whether clinical judgment or a calculation model is used, clinicians must decide if the clinical probability suggests further imaging studies, biopsy, and/or resection are needed

For seemingly benign nodules **(low probability of malignancy)**, an **accurate diagnosis** is required in

- TB or other infections requiring specific treatment
- Patients who are on high-dose immunosuppression

Solid, indeterminate nodule >8 mm in diameter with **moderate (5-60%) probability of malignancy** (when - **discordance between the clinical and radiologic features**)

- Consider functional imaging, preferably with **PET**, to **characterize the nodule** before surgical resection or continued radiological surveillance

Caveats :

- False-positive (e.g., TB, fungal and parasitic disease) and
- False-negative slow-growing tumors (eg, adenocarcinoma in situ)

- In an individual with a solid, indeterminate nodule >8 mm in diameter with **high (>60%) probability** of malignancy, functional imaging has a **greater role in preoperative staging than in characterizing the nodule**

- To rule out previously undetected metastases before surgical intervention

# Conclusion

- LC screening by LDCT scan reduces mortality (lung cancer specific and all cause mortality)
- Application of Lung-RADS and volumetric analysis reduces false positive rates
- In a moderate risk patient, use of PET/CT scan is less reliable and emphasis should be on non surgical biopsy
- Optimum screening interval, duration of screening and nodule measurements ?? - NELSON trial results