Review

Lung cancer screening trials:
Review of literature

Ioanna Tsiouprou,
Dionisios Spyratos,
Theodoros Kontakiotis

Pulmonary Department, Aristotle University of Thessaloniki, "G. Papanikolaou" Hospital, Exohi, Thessaloniki, Greece

Key words:
- Lung cancer
- Screening
- LDCT
- Mortality

SUMMARY
Lung cancer is considered one of the most common causes of morbidity and mortality globally. Survival depends mainly on clinical stage of the disease, histological type of lung cancer and patient's performance status. Implementation of a screening program among high-risk subjects might increase overall survival by increasing detection of lung cancers in early stages. In general an ideal screening program should be highly sensitive and specific, based on simple and safe examinations, cost effective and easily implemented. Low-dose computed tomography (LDCT) is currently the only proposed screening method for lung cancer. Based on the results of the National Lung Screening Trial (NLST), which was conducted in the USA and proved a 20% reduction in lung cancer specific related mortality, U.S. Preventive Services Task Force proposed official guidelines since 2014. In Europe there are no lung cancer screening recommendations/guidelines as the final results of the NELSON trial are still pending. The aim of this paper is to review the most important published trials on lung cancer screening.
Pneumon 2018, 31(3):159-166.

Correspondence:
Dionisios Spyratos
Assistant Professor of Pulmonary Medicine
Pulmonary Department, Aristotle University of Thessaloniki, Greece
Tel.: +30 6979490052
E-mail: dspyrato@auth.gr

INTRODUCTION

Lung cancer is considered one of the most common causes of morbidity and mortality globally[1]. Even though improvement has been achieved in treatment modalities (targeted agents, anti-angiogenetic factors and surgical approach with minimally invasive techniques), it remains the leading cause of cancer related death for both sexes worldwide.[1,2] It is estimated that 214,000 new lung cancer cases were diagnosed in Europe in 2012, while it is anticipated that new cases would be 222,500 in the USA during 2017.[2]

Survival depends mainly on clinical stage of the disease, histological type of lung cancer and patient's performance status. The 5-year survival rate for non small lung cancer (NSCLC) is about 92% for stage IA, 36% for those with IIIA and is almost zero for stage IVB.[3] On the other hand, the 5-year survival rate for small cell lung cancer (SCLC) is about 31% for localized disease,

8-19% in case of regional lymph nodes involvement and is only 2% for extended disease.[4]

Implementation of a screening program among high-risk subjects might increase overall survival by increasing detection of lung cancers in early stages. In general an ideal screening program should be highly sensitive and specific, based on simple and safe examinations, cost effective and easily implemented. The primary endpoint of a cancer screening program is the reduction of cancer-related mortality. Important parameters that should be carefully evaluated are: a) the number of participants needed to screen in order to prevent a lung cancer death, b) incidence and management of false positive results, c) the surgical-related morbidity/mortality of the detected cases, d) overdiagnosis (cases of early stage lung cancer that probably would not reduce survival especially among the elderly), e) anxiety and stress due to false positives and f) accessibility and cost.

In Europe there are no official lung cancer screening recommendations/guidelines. On the contrary, guidelines were published in the USA in 2014.[5-12] Low-dose computed tomography (LDCT) is currently the only proposed screening method for lung cancer. Undoubtedly the most important studies are the National Lung Screening Trial (NLST), which was conducted in the USA and its results affected nearly all guidelines, and the NELSON trial in Europe. The aim of this paper is to review the most important published trials on lung cancer screening.

We searched PubMed and Medline using the keywords: "Lung cancer" AND "screening" AND "mortality" as an initial criterion and mainly randomized studies were included in the present review.

SCREENING WITH CHEST X-RAY AND SPUTUM CYTOLOGY

Mayo Lung Project: It was a randomized controlled trial (1971-76) with prolonged follow up after the end of the trial. The study population included 9,211 males who underwent: chest x-rays and sputum cytology every 4 months for 6 consecutive years (intervention group) or advised to perform annual chest x-ray and sputum cytology in local healthcare units one (control).[13] After thirteen years of follow up there was no difference in lung cancer and all-cause mortality between groups.[13]

Memorial Sloan-Kettering study: This was also a randomized controlled trial (1974-78, USA).[13] All participants were men, current smokers, >45 years, who were randomly assigned to annual chest x-ray plus sputum cytology every 4 months vs annual chest x-ray. There was no significant difference for mortality rates between groups.[14]

Prostate, Lung, Colorectal, Ovarian cancer screening trial (PLCO): The PLCO trial was a randomized controlled multicentred study in the USA (1993-2001).[15,16] This was the largest (n=154,901) clinical trial that evaluated the role of chest x-ray as a screening tool. After thirteen years of follow up, there was no statistically significant difference for lung cancer related mortality (RR: 0.99, 95% CI: 0.91-1.07).[15,16]

A recent Cochrane meta-analysis exploring the role of chest x-ray showed that frequent screening with chest x-ray is accompanied with a trend for increased lung cancer related mortality (RR: 1.11).[12]

SCREENING WITH LDCT

National Lung Screening Trial (NLST): This was the largest randomized, controlled clinical study that evaluated the usefulness of LDCT as a screening tool and accomplished in 33 centers in the USA.[17] In this study, 53,454 participants (both sexes, age: 55-74 years, current/former smokers, ≥30 pack-years and quitted <15 years) were enrolled (8/2002 – 4/2004) and were followed up until 31/12/2009. Participants underwent annual LDCT for 3 years, whereas the control group was screened with chest x-ray. Any non-calcified nodule of ≥4mm on LDCT scans was considered positive/suspicious but no specific diagnostic/follow-up algorithm was used.[17]

Lung cancer related mortality was reduced by 20% in the intervention group (247 vs 309 deaths/100,000 person/year, relative reduction 20%, 95% CI: 6.8-26.7%, p=0.004). All-cause mortality decreased by 6.7% (95% CI: 1.2-13.6, p=0.02) and this was exclusively attributed to reduction of lung cancer mortality.[17] Nevertheless we should mention that the main disadvantage of this trial was the high rate of positive screening tests (false positive results: 96.4% intervention and 94,5% control group). The number needed to screen in order to prevent one lung cancer related death was 320. As the initial inclusion criteria were quite arbitrary a risk-model analysis was performed. The intervention group was divided into 5 quantities according to a validated prediction model for a 5-year risk of death because of lung cancer (Q1: 0,15-0,55%, Q5:>2%).[18] Parameters that were incorporated in this prediction model were: age, body-mass index, pack-years of smoking, years since smoking cessation,

TABLE 1. Large RCTs investigating lung cancer screening with LDCT

RCT	Sample size	Inclusion criteria	Control group	Screening interval	Follow up	Positive result for LDCT	Lung cancer related mortality	Main limitations
NLST (2002)	53,454	both sexes, 55-74 years old, current/ former smokers ≥30 pack-years and quitted <15 years	Chest X-ray	Annual	5 years	non-calcified ≥4mm, no specific diagnostic algorithm	20% reduction in the LDCT group	High rate of false positive tests
I-ELCAP (1993)	31,567	both sexes, >40 year-old, current/ former smokers, second-hand smokers history of occupational exposure, asymptomatic	no comparison	7-18 months	40 months	at least 1 non-calcified solid/ partly solid nodule ≥5mm or a non-solid, non-calcified nodule ≥8mm	no difference between baseline and annual screening	no specific follow up program
DANTE (2001)	2,472	males, 60-75 years old, current/ former smokers, ≥20 pack-years	Chest X-ray and sputum cytology at baseline	Annual clinical review	4 years	-	no significant difference	small sample size
DLCST (2004)	4,104	both sexes, 50-70 year old, current/ former smokers	Usual care (no intervention)	Annual	10 years	>15mm or those with rapid growth	No significant difference	overdiagnosis
MILD (2005)	4,099	both sexes, ≥50 year old, current/ former smokers, ≥20 pack-years	Usual care (no intervention)	Annual vs biennial	10 years	-	no significant difference	-
ITALUNG (2003)	3,206	both sexes, 55-69 year old, current/ ex-smokers, asymptomatic	Usual care(no intervention)	Annual	4 years	solid ≥8mm, significanr growth, new 3-5mm	-	overdiagnosis
LUSI (2007)	4,052	both sexes, 50-69 year old, current/ ex-smokers, ≥25 of 15 cigarettes/ day	Usual care(no intervention)	Annual	5 years	suspicious: ≥5mm, significant growth	no significant difference	early recall rates
UKLS (2011)	4,055	both sexes, 50-75 year old, >5% risk according to LLP risk model	usual care(no intervention)	LDCT at baseline	10 years	suspicious: >500mm^3 , part solid >100 mm^3	-	no mortality rate investigation
NELSON (2003)	15,822	both sexes, 50-75 year old, current/ former smokers, >15 cig./d for >25 years or >10 cig./d for >30 years	Usual care(no intervention)	PFTs and LDCT at baseline, LDCT after 1, 2 and 2,5 years	-	a standard protocol was developed	-	"healthy user bias"

the presence of emphysema and first-degree relative with lung cancer. It was concluded that 88% of the CT-prevented lung cancer deaths were included in the 60% of participants who constituted the high risk quintiles (Q3-Q5) and only 1% of the CT-prevented lung cancer deaths were detected within the lowest risk quintile (Q1).[17] Concerning the cost-effectiveness, the quality-adjusted life-year gained was $81,000.[19] However the anticipated health care cost in Europe would be considerably lower.

International Early Lung Cancer Action Program (I-ELCAP): The I-ELCAP program was a large scale (n=31,567), multicentered, international, uncontrolled study. All participants were asymptomatic, of both sexes, >40 year-old, current/former smokers (83%), second-hand smokers (11%), and/or had history of occupational exposure to asbestos, beryllium, uranium or radon (5%).[20-22] A baseline positive result was defined as either the presence of at least one non-calcified solid/partly solid nodule ≥5mm or a non-solid, non-calcified nodule ≥8mm. Thirteen percent had positive LDCT scan at baseline evaluation (1993-2005) and 405 of them (9.7%) were diagnosed with lung cancer. The number of participants with stage I was 412 (85%), while 375 underwent surgical resection with an estimated 10-year survival rate of 92% in case of resection during the first month after diagnosis.[23] It was actually the precursor for design and implementation of NLST.

Detection And Screening Of Early Lung Cancer By Novel Imaging Technology And Molecular Essays (Dante Trial): This was a randomized controlled trial that performed in Italy among 2,472 males (60-75 year old), current/former smokers with ≥20 pack-years.[24] Until January 2008 there was a median follow-up of 33.7 months. Even though the number of clinical stage I cases was significantly higher in the LDCT group (33 vs 12, p=0.004), there was no difference in lung cancer-specific mortality between the two groups (1.6 versus 1.7%, p=0,84).[24] Undoubtedly an important limitation was the small sample size. A more recent publication of this trial (8.35 years median follow-up) showed no significant difference in lung cancer related mortality.[25]

Danish Lung Cancer Screening Trial (DLCST): The DLCST trial was a randomized, multicenter, national, government funded trial.[26,27] A total number of 4,104 individuals (2,267 men) were enrolled in the clinical trial (10/2004-3/2006). They were current/former (abstinence <10 years, quitted after the age of 50) smokers aged 50-70 years. Nodules >15mm or those with rapid growth (volume increase >25% during a 3 months period or/and volume doubling time <400 days) were subjected to further diagnostic workup.[26] After an average follow-up of 9.5 years lung cancer-related mortality (HR: 1,03, 95% CI: 0,66–1,6; p = 0.888) as well as overall mortality had no significant difference between the two groups.[28] Lung cancer incidence was higher in the LDCT group which was attributed to higher number of early stage cases (stage I and II: 54 versus 10, p<0,001). An interesting finding was that smoking prevalence was reduced in both groups whereas psycho-social consequences were noted to be increased (better psycho-social profile in the LDCT group).[29,30]

Multi-Centric Italian Lung Detection Trial (MILD): This was a randomized, controlled, multicentered, national trial (n=4,099).[31] Participants were randomized into: annual screening, biennial and a control group. There was no difference in lung cancer related mortality rates among groups.[31] There was also no difference between annual and biennial LDCT screening regarding specificity, sensitivity, positive and negative predictive values for lung cancer diagnosis after 7 years of follow-up.[32]

Italian Lung Cancer CT Screening Trial (ITALUNG): It was a randomized controlled, multicentered trial that included 3,206 asymptomatic subjects.[33] Lung nodules were detected among 30.3% at baseline and after 4 annual screening rounds 23 out of 35 lung cancers were diagnosed at clinical stage I.

German Lung Cancer Screening Interventional Study (LUSI): This is an ongoing randomized, controlled trial with 4,052 participants.[34] Until 4/2014 fifty-eight lung cancer cases have been diagnosed after 4 completed rounds of LDCT. There was no difference between groups regarding overall mortality 3 years after randomization.[35]

United Kingdom Lung Cancer Screening Trial (UKLS): It is a randomized controlled trial planning to assess 30,000 individuals in order to evaluate LDCT effectiveness in a high-risk population.[36-39] In total, 4,055 individuals were randomized in the pilot trial.[37] The recruitment criteria were: age: 50-75 years and >5% risk of developing lung cancer according to a risk prediction model (Liverpool Lung Project (LLP) risk model v2, available on http://www.MylungRisk.org.).[38] In addition, a nodule management protocol was developed for the classification of CT findings (size, composition and VDT of nodules).[39]

Eventually 42 participants (2.1%) were diagnosed with lung cancer (34 at baseline and 8 at the 12-month scan), 85.7% were classified as clinical stage I or II and 83.3% underwent surgical resection.[37] Moreover, the baseline estimate for the incremental cost-effectiveness ratio rela-

tive to symptomatic presentation was 8,466£ per quality adjusted life year (QALY).

Dutch Belgian Randomized Lung Cancer Screening Trial (NELSON): It is the largest European randomized controlled trial. The primary endpoint is the reduction in lung cancer mortality and its final results are expected within the next few years.[40] With a statistical power of 80% to prove a reduction in lung cancer related mortality of 20-25% after 10 years of follow-up, 17,300-27,900 participants should be enrolled.[40] During the recruitment phase (12/2003-7/2006) 15,822 people of both sexes aged 50-75 years, current/former smokers (≤10 years of cessation, >15 cig./d for >25 years or >10 cig./d for >30 years) were randomized. Subjects of the intervention group underwent LDCT at baseline (first round), after 1 year (2nd), 2 years (3rd) and 2.5 years (4th, 5.5 years after baseline). PFTs were offered to the intervention group. All participants also received a quality of life questionnaire.[40-49]

A standard protocol was developed for the evaluation of the nodules detected in CT scan based its volume, composition and growth rate.[41] Results from the first three screening rounds showed that 209 participants were diagnosed with lung cancer: 70.8% of them were at clinical stage I and 51.2% of them were adenocarcinomas.[42]

After the first three rounds plus an additional 2 years of follow-up the sensitivity was 84.6% with a negative predictive value of 99.8% (196 screen-detected and 35 interval cancers).[43] Interval cancers were generally at a more advanced stage and most of them were SCLC.[43] Recent results reported that the interval cancers between the 3rd and 4th screenings were significantly more than those in the intervals of previous rounds (28 versus 5 and 28 versus 19).[44]

New solid nodules were detected among 11% of the participants after two screening rounds, 4% of these were malignant and correlated with nodule's volume (<27 mm^3: low risk, 27-206 mm^3: medium, >206 mm^3: high).[45]

Even though the "healthy user bias" was noted (eligible non responders were younger, more often former smokers and had higher level of physical exercise and education) it seems unlikely that these small differences will influence the generalizability of the NELSON trial.[46] Importantly smoking abstinence was more common among controls even though they had a lower prolonged abstinence rate compared to intervention (LDCT) group.[47] Even though increase in lung cancer specific distress was noted in participants who received an indeterminate baseline result there was no long term impact on health-related quality of life .[48,49]

CRITICAL ANALYSIS

During the year 2014 the U.S. Preventive Services Task Force (USPSTF) used modeling studies to predict the benefits and harms of screening programs that use different screening intervals, age groups and smoking histories.[5,6,11] According to their recommendation statement, LDCT lung cancer screening should be annually performed by adults between the age of 55 and 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued if a person has not smoked for 15 years or develops a health problem that significantly limits life's expectancy or the ability to undergo treatment or is unwilling to receive cancer treatment. Centers of Medicare and Medicaid Services organisation (CMS) cover the expenses of lung cancer screening with LDCT once per year for people aged 55-77 years, who are current or former smokers (≥30 pack-years) who have quit smoking within the last 15 years.[7]

Furthermore every organization affiliated with diagnosis and treatment of lung cancer in the USA (American Association for Thoracic Surgery[10], American Cancer Society[9,11], National Comprehensive Cancer Network[50]) have incorporated the results of NLST trial in their recommendations. The same criteria are suggested from the Canadian Task Force on Preventive Health Care.[51] Recently the European Society of Radiology in cooperation with the European Respiratory Society recommend that lung cancer screening should take place within a clinical trial or in routine clinical practice at certified multidisciplinary medical centres.[52,53]

In 2017, a European Union position statement on lung cancer screening was published.[54] It presented the current status of lung cancer screening, emphasizing on the outcomes of several lung cancer screening trials. According to the statement, It is crucial that a number of specific actions need to be adopted before the implementation of low-dose CT screening (eg risk stratification approach, detailed offer of information on the benefits and harms of screening, a smoking cessation program, use of semi-automatically measured volume and volume-doubling time for solid nodules, different protocols and multidisciplinary approach to nodules' management).

CONCLUSION

Lung cancer is a major public health problem worldwide. As the survival rates at earlier stages are higher,

the implementation of a screening program is highly necessary in order to reduce mortality rate.

The largest and most longstanding trials are the NLST trial for the United States, which showed a reduction of 20% in lung cancer related mortality and the NELSON trial for the European Union. Results of the NELSON trial are still pending in order to provide the scientific basis for the development of a lung cancer screening program across Europe. An effective screening program should be easily accessible, sensitive, specific, cost-effective, with low percentages of false positive and false negative results.

ΠΕΡΙΛΗΨΗ

Κλινικές μελέτες πρόληψης Καρκίνου του Πνεύμονα: Μία βιβλιογραφική ανασκόπηση

Ιωάννα Τσιούπρου, Διονύσιος Σπυράτος, Θεόδωρος Κοντακιώτης

Πνευμονολογικό Τμήμα, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης,
Π.Γ.Ν. "Γ. Παπανικολάου", Εξοχή, Θεσσαλονίκη

Ο καρκίνος του πνεύμονα θεωρείται μια από τις συχνότερες αιτίες νοσηρότητας και θνητότητας παγκοσμίως. Η επιβίωση εξαρτάται κυρίως από το κλινικό στάδιο της νόσου, τον ιστολογικό τύπο και τη λειτουργική κατάσταση του ασθενή. Η εφαρμογή προγραμμάτων πρόληψης σε άτομα υψηλού κινδύνου ίσως αυξήσει τη συνολική επιβίωση μέσω αύξησης της εντόπισης περιπτώσεων καρκίνου του πνεύμονα πρώιμου σταδίου. Γενικά ένα πρόγραμμα πρόληψης θα πρέπει να είναι εξαιρετικά ευαίσθητο και ειδικό, να βασίζεται σε απλές και ασφαλείς εξετάσεις, να έχει καλή σχέση κόστους-οφέλους και να είναι εύκολα εφαρμόσιμο. Η αξονική τομογραφία χαμηλής δόσης (LDCT) είναι η μόνη τρέχουσα προτεινόμενη μέθοδος προληπτικού ελέγχου για καρκίνο του πνεύμονα. Με βάση τα αποτελέσματα της National Lung Screening Trial (NLST), που διεξήχθη στις ΗΠΑ και έδειξε 20% μείωση της σχετιζόμενης με τον καρκίνο του πνεύμονα θνητότητας, η Υπηρεσία Πρόληψης των ΗΠΑ έχει προτείνει επίσημες οδηγίες από το 2014. Στην Ευρώπη δεν υπάρχουν συστάσεις/οδηγίες σχετικά με την πρόληψη του καρκίνου του πνεύμονα καθώς τα τελικά αποτελέσματα της μελέτης NELSON ακόμη αναμένονται. Στόχος της παρούσας εργασίας είναι η ανασκόπηση των πιο σημαντικών δημοσιευμένων μελετών σχετικά με τον προληπτικό έλεγχο στον καρκίνο του πνεύμονα.

Πνεύμων 2018, 31(3):159-166.

Λέξεις - Κλειδιά: *Καρκίνος πνεύμονα, πρόληψη, αξονική τομογραφία χαμηλής δόσης, θνητότητα*

REFERENCES

1. Global Burden of Disease Cancer Collaboration: Fitzmaurice C, Dicker D, Pain A, et al. The Global Burden of Cancer 2013. JAMA Oncol 2015;1:505-27.
2. World Health Organization. Cancer. Fact Sheet Number 297. http://www.who.int/mediacentre/factsheets/fs297/en/ Last updated February 2015. Date last accessed: February 10, 2015.
3. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:39-51.
4. American Society of Clinical Oncology (ASCO). Lung Cancer - Small Cell: Statistics. Approved by the Cancer. Net Editorial Board, 10/2016. Available at: http://www.cancer.net/cancer-types/lung-cancer-small-cell/statisticsLast updated: Aug 28, 2015, Last accessed: April 2, 2017.
5. Moyer V, U.S. Preventive Services Task Force. Screening for Lung Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2014;160:330-8.
6. Humphrey L, Deffebach M, Pappas M, et al. Screening for Lung Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation. AHRQ Publication 2013;13-05188-EF-1.
7. The Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Screening for Lung Cancer with Low Dose Computed Tomography (LDCT). 2015-02-05.
8. Black WC. Overdiagnosis: An underrecognized cause of confusion and harm in cancer screening. J Natl Cancer Inst 2000;92:1280-2.
9. Wender R, Fontham E, Barrera E, et al. American Cancer Society Lung Cancer Screening Guidelines. CA Cancer J Clin 2013;63:106-17.
10. Jaklitsch MT, Jacobson FL, Austin JH. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. Journal of Thoracic and

Cardiovascular Surgery 2012;144:33-8.
11. Smith RA, Andrews K, Brooks D, et al. Cancer screening in the United States, 2016: A review of current American Cancer Society guidelines and current issues in cancer screening. CA: A Cancer Journal for Clinicians 2016;66:96-114.
12. Manser R, Lethaby A, Irving LB, et al. Screening for lung cancer (Review). Cochrane Database Syst Rev 2013;(6):CD001991.
13. Marcus PM, Bergstralh EJ, Fagerstrom RM, et al. Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. J Natl Cancer Inst 2000;92:1308-16.
14. Melamed MR, Flehinger BJ, Zaman MB, et al. Screening for early lung cancer. Results of the Memorial Sloan-Kettering study in New York. Chest 1984;86:44-53.
15. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials 2000;21: 273S-309S.
16. Oken MM, Hocking WG, Kvale PA, et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. JAMA 2011;306:1865-73.
17. Aberle D, Adams A, Berg C, et al. Reduced Lung Cancer Mortality with Low-Dose Computed Tomographic Screening. N Engl J Med 2011;365:395-409.
18. Kovalchik S, Tammemagi M, Berg C, et al. Targeting of Low Dose CT Screening according to the risk of lung cancer death. N Engl J Med 2013;369:245-54.
19. Black W, Gareen I, Soneji S, et al. Cost- effectiveness of CT screening in the National Lung Screening Trial. N Engl J Med 2014;371:1793-802.
20. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999;354:99-105
21. Henschke CI, Naidich DP, Yankelevitz DF, et al. Early Lung Cancer Action Project: initial findings on repeat screenings. Cancer 2000;92:153-9.
22. Flieder DB, Vazquez M, Carter D, et al. Pathologic findings of lung tumors diagnosed on baseline CT screening. Am J Surg Pathol 2006;30:606-13.
23. International Early Lung Cancer Action Program Investigators; Henschke CI, Yankelevitz DF, Libby DM, et al. Survival of Patients with Stage I Lung Cancer Detected on CT Screening N Engl J Med 2006;355:1763-71.
24. Infante M, Cavuto S, Lutman FR, et al. A randomized study of lung cancer screening with spiral computed tomography. Three year Results from the DANTE Trial. Am J Respir Crit Care Med 2009;180:445-53.
25. Infante M, Cavuto S, Lutman FR, et al. Long-Term Follow-up Results of the DANTE Trial, a Randomized Study of Lung Cancer Screening with spiral computed tomography. Am J Resp Crit Care Med 2015;191:1166-75.
26. Pedersen J, Ashraf H, Dirksen A, et al. The Danish randomized Lung-cancer CT Screening Trial-overall design and results of the prevalence round. J Thorac Oncol 2009;4:608-14.
27. Saghir Z, Dirksen A, Ashraf H, et al. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. Thorax 2012;67:296-301.
28. Wille MM, Dirksen A, Ashraf H, et al. Results of the randomized danish lung cancer screening trial with focus on high-risk profiling. Am J Respir Crit Care Med 2016;193:542-51.
29. Rasmussen JF, Siersma V, Pedersen JH, et al. Psychosocial consequences in the Danish randomised controlled lung cancer screening trial (DLCST). Lung Cancer. 2015;87:65-72.
30. Ashraf H, Saghir Z, Dirksen A, et al. Smoking habits in the randomised Danish Lung Cancer Screening Trial with low-dose CT: final results after a 5-year screening program. Thorax 2014;69:574-9.
31. Pastorino U, Rossi M, Rosato V, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. Eur J Cancer Prev 2012;21:308-15.
32. Sverzellati N, Silva M, Calareso G, et al. Low-dose computed tomography for lung cancer screening: comparison of performance between annual and biennial screen. Eur Radiol 2016;26:3821-9.
33. Lopes Pegna A, Picozzi G, Falaschi F, et al. Four-year results of low-dose CT screening and nodule management in the ITALUNG trial. J Thorac Oncol 2013;8:866-75.
34. Becker N, Motsch E, Gross ML, et al. Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round. J Cancer Res Clin Oncol 2012;138:1475-86.
35. Becker N, Motsch E, Gross ML et al. Randomized Study on Early Detection of Lung Cancer with MSCT in Germany: Results of the First 3 Years of Follow-up after Randomization. J Thorac Oncol 2015;10:890-6.
36. McRonald F, Yadegarfar G, Baldwin D, et al. The UK Lung Screen (UKLS): Demographic profile of first 88,897 approaches provides recommendations for population screening. Cancer Prev Res 2014;7:362-71.
37. Field JK, Duffy SW, Baldwin DR, et al. UK Lung cancer RCT Pilot Screening Trial: Baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. Thorax 2016;71:161-70.
38. Raji O, Duffy S, Olorunshola M, et al. Predictive accurancy of the liverpool lung project risk model for stratifying patients for computed tomography screening for lung cancer: A case-control and cohort Validation Study. Ann Intern Med 2012;157:242-50.
39. Baldwin D, Duffy S, Wald N, et al. UK Lung Screen (UKLS) nodule management protocol: modeling of a single screen randomised controlled trial of low-dose CT screening for lung cancer. Thorax 2011;66:308-13.
40. Van Iersel C, De Koning H, Draisma G, et al. Risk-based selection from the general population in a screening trial: Selection criteria, recruitment and power fort the Dutch-Belgian randomized lung cancer multi-slice CT screening trial (NELSON). Int J Cancer 2006;120:868-74.
41. Van Klaveren RJ, Oudkerk M, Propok M, et al. Management of lung nodules detected by volume CT scanning. N Engl J Med 2009;361:2221-9.
42. Horeweg N, van der Aalst C, Thunnissen E, et al. Characteristics of lung cancers detected by computer tomography screening

in the randomized NELSON trial. Am J Respir Crit Care Med 2013;187:848-54.
43. Horeweg N, Scholten ET, De Jong PA, et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. Lancet Oncol 2014;15:1342-50.
44. Yousaf-Khan U, van der Aalst C, De Jong PA, et al. Final screening round of the NELSON lung cancer screening trial: the effect of a 2,5 year screening interval. Thorax 2017;72:48-56.
45. Walter JE, Heuvelmans MA, De Jong PA, et al. Occurence and lung cancer probability of new solid nodules at incidence screening with low- dose CT: analysis of data from the randomised, controlled NELSON trial. Lancet Oncol 2016;17:907-16.
46. Yousaf-Khan U, van der Aalst C, Horeweg N, et al. Baseline characteristics and mortality outcomes of control group participants and eligible non-responders in the NELSON lung cancer screening study. J Thorac Oncol. 2015;10: 747-53.
47. Van der Aalst CM, Van den Bergh KA, Willemsen MC, et al. Lung cancer screening and smoking abstinence: 2 year follow-up data from the Dutch Belgian randomized controlled lung cancer screening trial. Thorax 2010;65:600-5.
48. Van den Bergh KAM, Essink-Bot ML, Borsboom GJJM, et al. Long-term effects of lung cancer computed tomography screening on health-related quality of life: the NELSON trial. Eur Respir J 2011;38:154-61.
49. Van den Bergh K, Essink-Bot ML, Borsboom G, et al. Short term health related quality of life consequences in a lung cancer CT screening trial (NELSON). Br J Cancer 2010;102:27-34.
50. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Lung cancer screening. Version 2. 2016
51. Canadian Task Force on Preventive Health Care. Recommendations on screening for lung cancer. CMAJ 2016;188:425-32.
52. Kauczor HU, Bonomo L, Gaga M, et al. ESR/ERS white paper on lung cancer screening. Eur Respir J 2015;46:28-39.
53. Field JK, Devaraj A, Duffy SW, Baldwin DR. CT screening for lung cancer: Is the evidence strong enough? Lung Cancer 2016;91:29-35.
54. Oudkerk M, Devaraj A, Vliegenthart R, et al. European position statement on lung cancer screening. Lancet Oncol. Elsevier Ltd; 2017;18:e754–66.