ERJ Express. Published on February 13, 2014 as doi: 10.1183/09031936.00164513

Screening for lung cancer: time for large-scale screening by chest computed tomography

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ABSTRACT Lung cancer is the leading cause of cancer death worldwide. Age and smoking are the primary risk factors for lung cancer. Treatment based on surgical removal in the early stages of the disease results in better survival. Screening programmes for early detection that used chest radiography and sputum cytology failed to attain reduction of lung cancer mortality. Screening by low-dose computed tomography (CT) demonstrated high rates of early-stage lung cancer detection in a high-risk population. Nevertheless, no mortality advantage was manifested in small randomised control trials. A large randomised control trial in the USA, the National Lung Screening Trial (NLST), showed a significant relative reduction of 20% in lung cancer mortality and 6.7% reduction in total mortality, yet no reduction was evidenced in the late-stage prevalence. Screening for lung cancer by low-dose CT reveals a high level of false-positive lesions, which necessitates further noninvasive and invasive evaluations. Based primarily on the NLST eligible criteria, new guidelines have recently been developed by major relevant organisations. The overall recommendation coming out of this collective work calls for lung cancer screening by low-dose CT to be performed in medical centres manned by specialised multidisciplinary teams, as well as for a mandatory, pre-screening, comprehensive discussion with the patient about the risks and advantages involved in the process. Lung cancer screening is on the threshold of a new era, with ever more questions still left open to challenge future studies.

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Received: Sept 18 2013 | Accepted after revision: Dec 13 2013

Conflict of interest: None declared.

Introduction

Lung cancer causes 1.37 million deaths worldwide, which represents 18% of all cancer deaths, according to statistics for 2008 by the World Health Organization [1]. According to the National Cancer Institute (NCI), one in 15 men and women in the USA will be diagnosed with cancer of the lung and bronchus during their lifetime [2]. More individuals die from lung cancer than from colon, breast and prostate cancer combined. Surgical removal in the early stages is the most effective treatment of lung cancer, but early stages elude detection, because symptoms usually show at more advanced stages. Survival time thus decreases significantly with the stage of development of the disease, with a 5-year survival time declining from 50% for clinical stage IA to 43%, 36%, 25%, 19%, 7% and 2% for stages IB, IIA, IIB, IIIA, IIIB and IV, respectively [3]. Almost all patients with advanced lung cancer will die from the disease; it is therefore crucial to detect lung cancer early enough, before symptoms present themselves and while a cure through therapy is achievable.

The goal of screening is the increase of life expectancy and quality of life. However, decades of performing screening for lung cancer have produced no survival benefit. The Memorial Sloan-Kettering Study [4, 5] and the Johns Hopkins Study [6, 7], which evaluated adding sputum cytology to annual chest radiography, both failed to establish advantages in terms of survival time. The Mayo Lung Project was designed to appraise an intensive programme of chest radiographs and sputum cytology (taken every 4 months) compared with recommended annual chest radiography and sputum cytology [8–10]. After median follow-up of 20.5 years, an increased 5-year survival rate was found in the intervention arm, although lung-cancer specific mortality remained unchanged. In the Prostate, Lung, Colorectal and Ovarian cancer screening trial, participants were randomised to baseline and three annual (for smokers) or two annual (for never-smokers) posterior–anterior chest radiographs compared with the usual care [11]. From 1993 to 2001, over 150 000 participants at the ages of 55–74 years were enrolled. The data for lung cancer mortality, published in 2011, showed no benefits for chest radiology. Stage distribution and histology were similar in the two arms [12].

Screening results require careful analysis, as they are prone to distortions by several biases. These are: lead-time bias, where earlier diagnosis has no real effect on long-term outcome; length-time bias, where the screening programme will normally detect patients with slow-growing disease, whereas patients with aggressive disease may not be selected due to the rapid onset of symptoms and the disease progression; overdiagnosis, an extreme form of length-time bias, in which cancer that would never be clinically relevant is nevertheless treated; and other selection biases such as ''healthy volunteer''. Screening programmes are therefore not free of potential harms. This article will review the advantages as well as ill effects of screening in the short and long run. New guidelines for lung cancer screening by low-dose computed tomography (CT) have been published recently by several organisations according to updated data. In our review of the screening for lung cancer studies, we also wish to examine the course of action recommended by the various organisations in pursuit of a higher screening efficacy.

Single-arm low-dose CT screening trials

During the 1990s, studies of a single-arm low-dose CT screening were conducted in the USA [13, 14], Japan [15–17] and Germany [18]. The overarching result of these studies showed higher than expected lung cancer detection at early stages commensurate with the use of low-dose CT screening. In 2001, the first single-arm screening study of smokers and nonsmokers with low-dose CT, a 3-year study that started in 1996, was published by Sone *et al.* [15]. The study found that suspicious nodules were detected in relatively low prevalence: 279 (5.1%) of 5483 participants, in which 22 (8%) cases of lung cancer were confirmed surgically. Compared to the initial screening, repeat CT detected more aggressive, rapidly growing lung cancers. The third screening identified 88% (55 of 60) of lung cancer cases at stage 1A. According to the authors, nearly 11 times the expected annual number of early-stage cases was detected.

In 1993, Henschke and colleagues [13, 14] initiated the Early Lung Cancer Action Project study for early diagnosis of lung cancer. A thousand cigarette smokers 60 years of age or older underwent annual screenings with low-dose CT and chest radiography. Non-calcified nodules were detected in 23% participants by low-dose CT at baseline, compared with 7% by chest radiography. CT screening detected 27 (2.7%) with malignant disease, of which 23 (85%) were stage I, while only seven (0.7%) malignancies were detected by chest radiography, with four of them (57%) in stage I. Following these results, an international large study was initiated, the International Early Lung Cancer Action Program (IELCAP) [19]. This study, in which annual low-dose CT was used as a single arm, recruited 31 567 asymptomatic individuals at risk of lung cancer, aged 40–85 years, including second-hand smokers and persons vulnerable due to occupational exposure. An impressively high percentage of clinical stage-I lung cancer, 412 cases out of 484 (85%) malignant lesions, were detected at the baseline and annual screening. The IELCAP results were published in 2006 and opened the door to the introduction of annual low-dose CT screening for high-risk patients in

DOI: 10.1183/09031936.00164513

many medical centres, without any recommendations or guidelines to direct the expansion. These non-randomised controlled trials could not overcome the biases of selection, length time, lead time and overdiagnosis, and mortality data were unobtainable.

The year before, in 2005, a smaller trial, published by the Mayo clinic, questioned the benefit of lung cancer early detection programmes [20–22]. The trial compared the results of a 4-year study of screening with annual helical CT, to the 4-year follow-up of the Mayo Lung Project, which had been conducted during the 1970s and used chest radiology and sputum cytology [10]. The CT study included 1520 participants, in which lung cancer was detected in 31 (2%) at baseline (prevalence) CT and in 35 (2.3%) during follow-up (incidence and interval). Analysis for a more than 50% shift in the proportion of incidental stage-I nonsmall cell lung cancer (NSCLC) did not show statistical significance. Comparison of the CT study with the Mayo Lung Project in terms of lung cancer mortality rates and percentage of patients diagnosed with stage-I NSCLC and advanced-stage cancers, showed no statistically significant differences. Several other single-arm studies [23–26] demonstrated high percentage of early-stage lung cancer detection by low-dose CT screening, but offered no means of stage shift and mortality benefit evaluation.

A long follow-up trial of annual low-dose CT screening was conducted in Italy, in 2000, with 1035 participants [27]. After 7 years of screening, 33 of the 54 (61%) participants diagnosed had stage-I NSCLC [28]. Overall 5-year survival was 63% and mortality rate was lower than the expected rate in the Italian general population matched for age and sex (47 participants *versus* 75 expected). Also, lung cancer death rate was lower than expected for a matched population of US smokers (14 *versus* 27). These results of single-arm trials required evaluation by randomised control trials to overcome the various biases.

Randomised controlled trials

In the Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays (DANTE) trial, 2472 patients were randomised for annual spiral CT *versus* a clinical review for 4 years [29]. Stage-I lung cancer detection rate was four-fold higher with spiral CT; 16 out of 28 (57%) *versus* four out of eight (50%) patients checked by baseline chest radiograph in the control group. The effect of CT screening on mortality was published in 2009 [30]. After a mean follow-up of 33 months, the number of advanced lung cancer cases, lung cancer mortality and other causes mortality in the two arms was the same.

In the same year, a larger randomised controlled trial, the Danish Lung Cancer Screening Trial (DLCST), reported the results of low-dose CT screening on stage detection and mortality [31, 32]. Annual CT for 5 years diagnosed more lung cancer (69 of 2052) than the usual care (24 of 2052; $p<0.001$) and at earlier stages of NSCLC. However, the frequency of diagnosis at later stages showed no statistically significant difference between the screening and the control groups, after a median follow-up of 4.81 and 4.77 years, respectively. Furthermore, mortality from lung cancer and of all causes was higher in the screening group, although these differences were not statistically significant. This finding, in which no stage shift was demonstrated, implies overdiagnosis bias. In future, results of DLCST will combine with the Dutch–Belgian NELSON (NEderlands Leuvens longkanker Screenings ONderzoek) trial for a total of about 20 000 participants.

The NELSON trial was designed to establish the optimal way in which follow-up screening must be conducted in order to reduce mortality [33–35]. Low-dose CT was performed at year 1, 2 and 4 in high-risk participants at the ages of 50–75 years *versus* usual care in the control arm. In the first screening, lung cancer was detected in 70 (0.9%) participants, of which 63.9% were in stage I. In the second round, 54 (0.7%) of 7289 participants were diagnosed with lung cancer, of which 73.7% were at stage I. The effect of low-dose CT screening on mortality is still under evaluation.

After 4 years of annually performing low-dose CT screening, compared with the usual care practice in the ITALUNG trial [36, 37], NSCLC was diagnosed in 35 of the 1406 participants in the low-dose CT group (2.5%), in whom 23 (65.7%) were stage I. Stage shift calculations were not published and mortality data are not expected till 2014.

The need to establish a proven clinical advantage in mortality reduction, of low-dose CT screening over the risks of undesirable outcomes, called for a large prospective randomised controlled trials. In the USA, the NCI, which conducted a pilot study, in collaboration with the Lung Screening Study (LSS) [38, 39], and the American College of Radiology Imaging Network, set up the large-scale National Lung Screening Trial (NLST). This trial was terminated in October 2010, when the Data and Safety Monitoring Board of the NLST concluded that enough data had been collected for the primary goal of the trial to be achieved [40]. The results of the NLST were published in 2011 [41], and follow-up data on the first screening round were issued 2 years later [42]. The primary end-point of the study was to assess lung cancer mortality [43]. High-risk, 55- to 74-year-old patients with at least 30 pack-years' smoking history, who were still active smokers, or former smokers that quit within the previous 15 years, were randomised to undergo annual low-dose CT

screenings compared with chest radiography for 3 years. Between 2002 and 2004, a total of 53 454 participants from 33 US medical centres were enrolled on the programme and were followed up until 2009. Incidence of lung cancer was 13% higher in the low-dose CT group (645 cases per 100 000 person-years), as compared with the radiography group (572 cases per 100 000 person-years). The rate of death from lung cancer was relatively reduced by 20% (95% CI 6.8–26.7%; p=0.004) in the low-dose CT group (247 *versus* 309 per 100 000 person-years). The overall death rate was reduced in the low-dose CT group by 6.7% (95% CI 1.2–13.6%; p=0.02) as compared with the radiography group. For one case of death from lung cancer to be prevented, out of those who underwent at least one screening, the number of patients needed to be screened in low-dose CT compared to chest radiology was 320. For positive screening, *i.e.* nodule suspicious for lung cancer, stage I disease was detected in 63% in the low-dose CT group compared to 47.6% in the chest radiography group. However, there was no statistically significant difference between the CT and chest radiography groups in the advanced stages (IIB–IV) detection rate. Adenocarcinomas, including the low grade of what was formerly called "bronchioloalveolar" carcinoma (BAC), were predominant in early stages in both screening modalities but higher in the low-dose CT group. Significant reduction in lung cancer mortality, as demonstrated exclusively by the NLST, lowers the magnitude of lead- and length-time biases, something which the smaller randomised controlled trials were unable to accomplish, for lack of statistical power. Disease-specific mortality reduction is the most conclusive indicator of the benefits of screening. The mortality reduction measure provides the net effect of screening regardless of the length of time recorded from diagnosis to death. Randomisation of a large population together with long-term follow-up can scientifically lower selection biases, although the magnitude of this reduction is currently unknown.

Following the NSLT, a retrospective risk stratification model was constructed to help raise the yield of low-dose CT screening results [44]. Based on selected predictors for lung cancer death, which were picked from a set of previously identified demographic and clinical risk factors of lung cancer, participants were stratified into five quintiles for the predicted 5-year risk of death from lung cancer. Quintile 1 had the lowest risk of death in 5 years, ranging from 0.15 to 0.55%, while quintile 5 had the highest risk of more than 2%. The number of lung cancer deaths per 10 000 person-years that were averted by low-dose CT screening in the NLST trial increased significantly across the risk quintiles, starting from 0.2 in quintile 1, to 12.0 in quintile 5 (p=0.01 for trend). The number of patients needed to screen in order to prevent one death from lung cancer decreases along the quintiles, from 5276 in quintile 1 to 161 in quintile 5 (p<0.001 for trend). Moreover, false-positive results of screening were significantly lower in quintile 5 (88%) compared with quintile 1 (97%). The ratio of harms to benefits, represented by the ratio of the number of participants with false-positive results to the number of CT-prevented lung cancer deaths, decreased significantly across the risk quintiles, from 1648 in quintile 1 compared to 65 in quintile 5 (p<0.001 for trend).

Differences of study protocols

Difference of results depending on the study could be partially explained by differences of the screened population, geographical area, study design and follow-up protocols. Table 1 summarises the major differences of low-dose CT screening trials in high-risk participants, with more than 1000 individuals in the low-dose CT arm. Different selection criteria of age, sex, risk factors, as well as differences of CT collimation, frequency and duration of screening and follow-up, could give rise to outcome discrepancies. Moreover, there is diversity in the definition of positive CT results, different protocols, or lack of protocol, for nodule management, and varied settings in which decisions are made. These elements are summarised in table 2. Studies apply different ways of measuring and hence of defining a "nodule". Some studies base their measurement on average diameters [13, 20, 25, 26, 36], others use maximal diameters [23, 27, 28, 31, 43, 45, 46], and yet others, such as the NELSON and the Multicentric Italian Lung Detection studies [34, 45], employ the volumetric measurement. The size of a nodule considered "positive" vary between "any" nodule [20], a nodule of at least 4–5 mm in diameter in most studies, and a nodule of at least 10 mm in the DANTE trial [29], unless it has speculated margins. Most trials put guidelines in place for nodule management in cases of positive results in the basic screening, and cases of growth or new nodules in incidence screening. In most trials, evaluation was managed at the centre in which the study was based, however in the LSS [38, 39] and the German Lung Cancer Screening Intervention trial (LUSI) [46] screening results were mailed to patients, and in the NLST [43] results were sent to the participants and their healthcare providers with recommendations by the medical centre radiologist for follow-up evaluation.

Low-dose CT screening detection rates

For baseline screening, positive results in the major single-arm trials were found in 11–51% of participants, according to the study protocol. Detection rate of lung cancer ranged between 1.1–2% in baseline screening and false-positive rates of 90–96%. In the Mayo Clinic Study [20, 21], a positive test (any nodule) was found in 780 of 1520 (51%) participants, but nodules of above 4 mm were detected in 435 (29%) of the study

DOI: 10.1183/09031936.00164513

TABLE 1 Summary of low-dose computed tomography (CT) screening trials of high-risk participants[#]

Study	Country	Accrual/last screening[¶]	Baseline screening participants (randomised)	Low-dose CT timing	CT collimation mm	Age years	Males %	Risk factors
Single-arm trials								
SWENSEN [21, 22], 2003, 2005	USA	1999/2003	1520	Annual 5 years	5	50–85	52	Smoking: ⩾20 PY; active or quit <10 years
PASTORINO [27], 2003; VERONESI [28], 2010	Italy	2000/2008	1035	Annual 7 years	10	⩾50	71	Smoking: ⩾20 PY
HENSCHKE [19], 2006 (IELCAP)	International: USA, Europe, Japan, China, Israel	1993–2005/2005	31 567	Annual	NR[+]	40–85	NR	Any smokers; ex-smokers; passive smokers; occupational exposure[§]
VERONESI [23, 24], 2008	Italy	2004–2005/2006	5201	Baseline and 1 year later	2.5	⩾50	66	Smoking: ⩾20 PY; active or quit <10 years
WILSON [25], 2008 (PLuSS)	USA	2002–2005/2006	3642 (3755)	Baseline and 1 year later	2.5	50–79	51	12.5 years[f]; if quit <10 years
MENEZES [26], 2010	Canada	2003–2007/2008[##]	3352	Annual	1–1.25	50–80	46	Any smoking history of ⩾10 PY
Randomised controlled trials								
DANTE [29, 30], 2008, 2009	Italy	2001–2006/2008	2472: CT 1276 (1403); control 1196 (1408)	Annual CT 5 years *versus* usual care	5	60–74	100	Smoking: ⩾20 PY; active or quit <10 years
DLCST [31, 32], 2009, 2012	Denmark	2004–2006/2010	4104: CT 2052 (2052); control 2052 (2052)	Annual CT 5 years *versus* usual care	0.75	50–70	55	Smoking: ⩾20 PY; active or quit <10 years after age 50 years
NELSON [34, 47, 48], 2006, 2009, 2013	The Netherlands, Belgium	2004–2006/2008[¶¶]	15 822: CT 7557 (7915); control 7907 (7907)	Low-dose CT in years 1, 2, 4 *versus* no screen	0.75	50–75	84	15 PY[++]; quit ⩽10 years
ITALUNG [36, 37], 2009, 2013	ITALY	2004–2006/2010	3206: CT 1406 (1613); control 1593 (1593)	Annual CT 4 years *versus* usual care	0.75–3	55–69	65	Smoking: ⩾20 PY; quit ⩽10 years
LSS [38, 39], 2004, 2005	USA	2000/2001	3318: CT 1586 (1660); rad. 1550 (1658)	Baseline CT and 1 year later *versus* rad.	5	55–74	58	Smoking: ⩾30 PY; quit ⩽10 years
NLST [41–43], 2011, 2013	USA	2002–2004/2007	53 454: CT 2639 (26 722), rad. 2605 (26 732)	Annual CT 3 years *versus* rad.	⩽2.5	55–74	59	Smoking: ⩾30 PY; quit ⩽15 years
MILD [45], 2012	Italy	2005–2011/2011	4099: Annual CT 1152 (1190); biannual CT 1149 (1186); control 1723 (1723)	Annual CT *versus* biannual CT *versus* control	1	⩾49	66	Smoking: ⩾20 PY; quit ⩽10 years
LUSI [46], 2012	Germany	2007–2011/2012	4052: CT 2029; Control 2023	Annual CT 4 years *versus* usual care	1	50–69	65	15 PY++; quit ⩽10 years

PY: pack-years; NR: not reported; rad.: radiograph. [#]: with criterion of more than 1000 participants in the low-dose CT arm; [¶]: year in which accrual screening was carried out/last year of screening (at time of latest publication); [+]: paper referring to the protocol on IELCAP website with the latest protocol (July 1, 2011); in ELCAP, 10 mm; [§]: asbestos, beryllium, uranium or radon; [f]: at least one half-pack per day for at least 25 years; [##]: "to date" paper received January 2009; [¶¶]: second round; [++]: more than 15 cigarettes a day for more than 25 years, or more than 10 cigarettes a day for more than 30 years.

TABLE 2 Summary of low-dose computed tomography (CT) screening trials of high-risk participants according to method of nodule measurement and definition of positive CT results, protocol for nodule management, and varied settings in which decisions are made

Study	Nodule measurement	Positive non-calcified nodule#	Evaluation of non-calcified lesion according to nodule size	Growth criteria for malignancy	New nodule or change or repeat CT	Decision of work-up
Single-arm trials						
SWENSEN [21, 22], 2003, 2005	Average of the largest and perpendicular transverse diameters	Any	Recommended: >4 mm: repeat CT in 6 months 4–7 mm: repeat CT in 3 months 8–20 mm: CT nodule enhancement protocol or PET >20 mm: CT, PET biopsy or removal indicated	NR	NR	Letter with recommendations from investigators to patient and physician
PASTORINO [27], 2003; VERONESI [28], 2010	Maximum diameter	>5 mm	>5 mm: thin-section CT of 1 mm with 3D analysis and contrast enhancement if density of >0 HU If ⩾ 7 mm: also PET If ⩾ 7 mm with positive contrast enhancement or positive PET: biopsy	NR	NR	Recommendations were made according to protocol by the radiologists
HENSCHKE [19], 2006 (IELCAP)	Average of length and width	Solid >5 mm; non-solid >8 mm	Recommended: 5–14 mm: repeat CT in 3 months or PET; if growth or PET positive: biopsy or FNA >14 mm: biopsy or PET or repeat CT in 3 months	NR	<3 mm: repeat CT in 6 months 3–5 mm: repeat CT 3 months >5 mm: antibiotics for 2 weeks; repeat CT 1 month No resolution or growth: biopsy or PET; if negative, repeat CT 3 months	By patient and physician
VERONESI [23, 24], 2008	Maximum axial diameter	>5 mm	5.1–8 mm: repeat CT in 3 months >8 mm (unless clearly benign appearance): PET or enhancement CT Suspected malignancy: diagnostic procedure Suspected infection: antibiotics for 10 days, repeat CT in 1–3 months	VDT 30–400 days	If <8 mm: PET or enhancement CT Benign characteristics: repeat CT in 3 months	MDT
WILSON [25], 2008 (PLuSS)	Average of the largest and perpendicular transverse diameters	>5 mm	Recommended: ⩽4 mm: during first year repeat CT in 6 months, no further evaluation 5–9 mm without spiculations: CT or PET or repeat CT in up to 3 months 5–9 mm with spiculations or >9 mm: diagnostic procedure	Increase in size or density or any other suspicious change	NR	MDT written report with recommendations sent to patient and personal physician

DOI: 10.1183/09031936.00164513

TABLE 2 Continued

Study	Nodule measurement	Positive non-calcified nodule#	Evaluation of non-calcified lesion according to nodule size	Growth criteria for malignancy	New nodule or change or repeat CT	Decision of work-up
MENEZES [26], 2010	According to IELCAP protocol		5–14 mm: repeat CT in 3 months ⩾15 mm: biopsy or antibiotics and repeat CT in 1 month	Any	<3 mm: repeat CT in 6 months 3–5 mm: repeat CT in 3 months >5 mm: repeat CT in 1 month	NR
Randomised controlled trials						
DANTE [29, 30], 2008, 2009	Diameter	⩾10 mm; <10 mm with spiculated margins	Recommended: 6–9 mm with smooth surface: repeat CT in 3, 6, 12 months 6–9 mm: antibiotics; HRCT after 6–8 weeks; if no regression, a case-by-case evaluation and consideration of invasive procedure 10–20 mm: HRCT after 6–8 weeks; if no regression, PET or case-by-case evaluation and consideration of invasive procedure >20 mm: oral antibiotics and HRCT or standard contrast-enhanced CT and PET scan; if positive: diagnostic procedure	NR	Case-by-case evaluation	By clinician
DLCST [31, 32], 2009, 2012	Maximal diameter	>4 mm except if benign characteristics	5–15 mm: repeat CT in 3 months >15 mm: diagnostic procedure	Increase in volume by 25%: diagnostic procedure	NR	Conferences between a pulmonologist and the radiologists
NELSON [34, 47, 48], 2006, 2009, 2013	Volume (automated software)	NODCAT 3–4: solid or solid component: >50 mm^3; solid, pleural based: 5 mm; non-solid, pure or component: ⩾8 mm	NODCAT 3: repeat CT at 3 months; if no growth, annual repeat CT in 8–9 months NODCAT 4: volume >500 mm^3 or pleural based >10 mm: diagnostic procedure	VDT <400 days or new solid component in a non-solid lesion: diagnostic procedure	NODCAT 3: repeat CT in 6–8 weeks; if growth, refer to chest physician NODCAT 4: refer to chest physician	MDT

TABLE 2 Continued

Study	Nodule measurement	Positive non-calcified nodule#	Evaluation of non-calcified lesion according to nodule size	Growth criteria for malignancy	New nodule or change or repeat CT	Decision of work-up
ITALUNG [36, 37], 2009, 2013	Mean diameter	Solid: 5 mm; non-solid: 10 mm; any part-solid nodule	5–7 mm: repeat CT in 3 months; if growth, PET or tissue diagnosis ⩾8 mm: PET; if positive, FNA; if negative, CT in 3 months Inflammatory appearance: repeat CT in 1 month; if no complete resolution, repeat CT in 2 months or PET and consider diagnostic procedure	⩾1 mm	⩽3 mm: repeat CT in 6 months >3 to <5 mm: repeat CT in 3 months ⩾5 mm or inflammatory appearance: antibiotics, repeat CT in 1 month; if no complete resolution, repeat CT in 2 months Pure non-solid ⩾10 mm or new non-solid or part solid ⩾8 mm: if persisted after antibiotics, CT-guided FNAB	Not specified
LSS [38, 39], 2004, 2005	Diameter (NR)	⩾4 mm or any spiculated nodule	No protocol	No protocol	No protocol	Evaluation by healthcare provider, referral to specialist was optional
NLST [41–43], 2011, 2013	Maximum diameter	⩾4 mm	No uniform protocol¶	No uniform protocol¶	No uniform protocol¶	Recommendations were sent to patients by NLST radiologists; evaluation by healthcare provider
MILD [45], 2012	Volume or diameter	⩾60 mm^3 or ⩾4.8 mm	60–250 mm^3 or 5–8 mm: repeat CT in 3 months 250 mm^3: PET and/or biopsy	Volume >25% in 3 months: further evaluation	NR	Not specified
LUSI [46], 2012	Average of length and width (according to IELCAP protocol)	⩾5 mm	5–7 mm: repeat CT in 6 months for VDT measurement 8–10 mm: repeat CT in 3 months for VDT measurement >10 mm: highly suspicious for malignancy, immediate recall; if not, repeat CT in 3 months	VDT 400–600 days or VDT ⩽400 days and nodule diameter>10 mm: immediate recall	No specific protocol; evaluated by office-based pulmonologist	Reports were sent to participants to contact a physician of choice for further advice

PET: positron emission tomography; NR: not reported; FNA: fine-needle aspiration; VDT: volume doubling time; MTD: multidisciplinary team; HRCT: high-resolution CT; NODCAT: nodule category (based on size). #: or suspicious calcification such as speckled or peripheral; ¶: some centres developed practice guidelines.

DOI: 10.1183/09031936.00164513

population. Lung cancer was detected by CT in 30 (2%) at baseline screening and 32 (2%) in the following 4 years, while interval lung cancer (diagnosed by symptoms) was found in three (0.2%). Stage I was found in 21 out of 31 (68%) participants in the baseline screening. Rates of false-positive findings, of non-calcified nodules of more than 4 mm in average diameter, were 92.9% and 92.4% for the prevalence and incidence screening, respectively. A total of 69% of the participants had at least one false-positive finding after five annual low-dose CT screenings. Lower rates of positive results were found in the IELCAP trial [19]. Out of the 31 567 participants, 4186 (13%) were found positive in the baseline screening, of which 405 (1.3%) were diagnosed as lung cancer. Incident lung cancer was found in 74 of 27 456 (0.3%) in annual low-dose CT screenings performed between 1994 and 2005 (median 2002), and interval (interim) lung cancer was found in five (0.02%). This finding represents a false-positive rate of 90% (3781 cases) in the baseline screening. As mentioned above, with respect to clinical stage-I lung cancer, 412 out of 484 (85%) malignant lesions were detected at the baseline and annual screening.

Table 3 summarises the main findings of CT screening by the major randomised controlled trials. Positive results in the baseline screening ranged between 8.7% in the DLCST [31, 32] to 30.3% in the ITALUNG trial [36, 37]. This disparity could be partly the result of the diverse classifications of ''positive nodule'' (table 2). In the ITALUNG trial, any non-calcified nodule measuring 5 mm or more in mean diameter was classified positive, whereas the DLCST classified as negative finding any nodule with benign appearance measuring more than 5 mm in maximal diameter. In the NELSON trial, positive results were defined as NODCAT 4, while indeterminate lesions (NODCAT 3), although further evaluated by repeat screening after 3 months (as was the practice in most trials where indeterminate lesions were classified as positive results), were not considered as positive in the final calculations [34, 35, 48]. The reported low positive and low false-positive screening rates of the NELSON trial should therefore be qualified accordingly. In table 3, the indeterminate and positive lesions findings of the NELSON trial have been combined together, so that the information compares better with the results of other studies.

The rate of lung cancer detected in the baseline CT ranged between 0.8% of the screened population in DLCST [31, 32] to 2.2% in the DANTE trial [29, 30]. In the NLST [41, 42], which represents the largest population screened, prevalence of lung cancer was 1.1%. Prevalence of stage-I lung cancer in the baseline CT ranged between 48% in the ITALUNG trial [36, 37] to 82% in the LUSI trial [13, 14, 19]. In the NLST, out of the 292 lung cancer cases diagnosed after the baseline CT screening, 270 (1%) participants were with positive lesions on CT. Stage-I lung cancer was detected in 155 of 266 (58.3%) participants with known stage in the positive baseline CT group. After three screening rounds, 415 of 720 (58%) participants in the low-dose CT arm had stage-I lung cancer, and of those with a positive CT screening, 400 out of 635 (63%) were participants with stage I. For baseline CT, sensitivity and specificity were 93.8% and 73.4%, respectively.

In the NELSON study [34], sensitivity of the baseline screening for lung cancer detection was 94.6%, specificity 98.3%, positive predictive value 35.7%, and negative predictive value was 99.9%. Incidence of lung cancer was another element calculated in the NELSON study. The probability of finding lung cancer was one case in 1000 1 year after a negative baseline test and three in 1000 after 2 years. An update of results from the NELSON trial was published in 2013 [48]. After the three screening rounds, lung cancer was detected in 200 (2.6%) of the 7582 participants who were actually screened. In order to detect one lung cancer, 38 participants underwent three screening rounds. A 5.5-year lung cancer risk calculations after negative, indeterminate and positive baseline screening were 1%, 5.7% and 48.3%, respectively. Stage distribution and histology were not reported.

Major concerns

False-positives

A major concern of any screening programme is the false-positive rate. False-positive findings lead to unnecessary further evaluations and are implicated in the ensuing complications and patient's anxiety. False-positive results are the product of the difference between positive CT results according to the study protocol and lung cancer detection rates. In baseline screening, false-positive results ranged between 86% in the DANTE trial [29, 30, 45] to 96% in the NLST [41, 42] and LUSI trial [46]. Following the LSS results [38, 39], the cumulative risk of receiving at least one false-positive result or unnecessary diagnostic procedure was calculated for patients who participated in a 1- or 2-year lung cancer screening examination [49]. The study found a 21% cumulative probability of one or more false-positive result after one screening and 33% after two screenings by low-dose CT. The chance of false-positive results for examination by chest radiography was 9% after one screening and 15% after two screenings. Invasive procedures resulted in a total of 7% and 4% of participants with a false-positive low-dose CT and chest radiography, respectively. In order to reduce unnecessary investigations, we believe that biomarker panels are set to increase our ability to identify lung cancer in cases of suspected nodules among patients on low-dose CT, which will also enhance

TABLE 3 Computed tomography (CT) screening results by major randomised control trials (with more than 1000 participants in each arm)

Study	Randomised	Screened at baseline n (%)	Follow-up: annual screenings years	Positive CT according to study protocol %			False-positive preval. %	Lung cancer[#] %			AdenoCA+ BAC[¶] %	Stage I[¶] %			Mortality %	
				Preval.	Incid.	Total		Preval.	Incid.	Total		Preval.	Incid.	Total	Total	Lung cancer
DANTE [29, 30], 2008, 2009	2472		2.81[+,§]		4 rounds				4 rounds				4 rounds			
CT	1403	1276[ƒ] (90.9)	2.98[+]	199 (15.6)	152 (11.9)	351 (27.5)	171 (86)	28 (2.2)	32 (2.5)	60 (4.7)	27/63 (43)	16/28[##] (57.1)	17/32 (53.1)	33/60 (55)	46 (3.6)	20 (1.6)
Control	1196		2.63[+]	45 (3.8)	108[¶¶] (9)	153 (13)	37 (82.2)	8 (0.7)	26 (2.2)	34 (2.8)	13/36 (36)	4/8 (50)	8/26 (30.8)	12/34 (35.3)	45 (3.8)	20 (1.7)
DLCST [31, 32], 2009, 2012	4104				4 rounds				4 rounds				4 rounds			
CT	2052	2052 (100)	4.81[+]	179 (8.7)	432 (21.1)	611 (29.8)	162 (90.5)	17 (0.83)	52 (2.5)	69 (3.4)	48/69 (70)	9/17 (52.9)	37/50[++] (74)	46/69 (66.7)	61 (3)	15 (0.7)
Control	2052		4.77[+]					1[§§] (0.05)	23 (1.1)	24 (1.2)	10/24 (42)	1/1 (100)	4/17[++] (23.5)	5/18 (20.8)	42 (2)	11 (0.5)
NELSON [34, 47, 48], 2006, 2009, 2013	15 822		2.15[ƒƒ]		2nd round				2nd round				2nd round			
CT	7915	7557 (95.5)	2	1571[###] (20.8)	1130[###] (14.2)	2701[###,¶¶¶] (35.6)	1493[+++] (95.1)	70 (0.9)	130 (1.6)	200[¶¶¶] (2.6)	NR	46/72[§§§] (63.9)	42/57 (73.7)	88/129 (68.2)		
Control	7907															
ITALUNG [36, 37], 2009, 2013	3206		4		3 rounds				3 rounds				3 rounds			
CT	1613	1406 (87.2)		426 (30.3)	NR (avg. 15.7%)	NR	406 (95.3)	21[ƒƒƒ] (1.5)	18 (1.2)	39 (2.8)	25/38 (66)	10/21 (47.6)	13/17 (76.5)	23/35 (65.7)		
Control	1593															
LSS [38, 39], 2004, 2005	3318				2nd round				2nd round				2nd round			
CT	1660	1586 (95.6)	1	325 (20.5)	360[####] (25.8)	685 (43.2)	295 (90.1)	30 (1.9)	8 (0.6)	38 (2.3)	24/40 (60)	16/30 (53.3)	2/8 (25)	18/38 (47.4)		
Radiograph	1658	1550 (93.5)		152 (9.8)	115[¶¶¶¶] (8.7)	267 (17.2)	145 (95.4)	7 (0.5)	9 (0.7)	16 (1)	9/45 (20)	6/7 (85.7)	2/9 (22.2)	8/6 (50)		
NLST[41, 42], 2011, 2013	53 454		6.5[+]		2 rounds				2nd round				2 rounds			
CT	26 722	26 309 (98.5)		7191 (27.3)	10955 (22.4)	NR (39.1)	6921[++++] (96.2)	270[§§§§] (1)	379[§§§§] (1.4)	649[§§§§] (2.4)	490/1048 (47)	155/266[ƒƒƒƒ] (58.3)	245/369[ƒƒƒƒ] (66.4)	400/635[ƒƒƒƒ] (63)	1877[#####] (7)	356[#####] (1.3)
Radiograph	26 732	26 035 (97.4)		2387 (9.2)	2656 (5.6)	NR (16)	2251[++++] (94.3)	136[§§§§] (0.5)	143[§§§§] (0.5)	279[§§§§] (1)	363/931 (39)	62/133[ƒƒƒƒ] (46.6)	69/142[ƒƒƒƒ] (48.6)	131/275[ƒƒƒƒ] (47.6)	2000[#####] (7.5)	443[#####] (1.7)

DOI: 10.1183/09031936.00164513

TABLE 3 Continued

Study	Randomised	Screened at baseline n (%)	Follow-up: annual screenings years	Positive CT according to study protocol %			False-positive preval. %	Lung cancer# %			AdenoCA+ BAC¶ %	Stage I¶ %			Mortality %	
				Preval.	Incid.	Total		Preval.	Incid.	Total		Preval.	Incid.	Total	Total	Lung cancer
Mild [45], 2011	4099		4.4+													
Annual CT	1190	1152¶¶¶¶¶ (96.8)		177 (14.9)	NR	NR	166 (93.4)	11 (0.9)	18 (1.5)	29 (2.4)	15/29 (51.7)	NR	NR	18/29 (62.1)	31 (2.7)	12 (1)
Biannual CT	1186	1149¶¶¶¶¶ (96.9)		158 (13.3)	NR	NR	152 (96.2)	6 (0.5)	14 (1.2)	20 (1.7)	17/20 (85)	NR	NR	14/20 (70)	20 (1.7)	6 (0.5)
Control	1723									20 (1.2)	32/49 (65.3)				20 (1.2)	7 (0.4)
Lusi [46], 2012	4052		NR													
CT	2029	2029 (100)		540 (26.6)	NR	NR	518 (95.9)	22 (1.1)	NR	NR	15/22 (68.2)	18/22 (81.8)	NR	NR		
Control	2023															

AdenoCA: adenocarcinoma; BAC: bronchioalveolar carcinoma; preval.: prevalence; incid.: incidence; NR: not reported; avg.: average. #: including small cell lung carcinoma; ¶: of all lung cancer cases, including small cell lung carcinoma; +: median years; §: 161 subjects (6.5%) having ⩾5 years of follow-up; ƒ: chest radiography and sputum cytology at baseline; ##: including one patient detected only by positive sputum cytology and bronchoscopy; ¶¶: by clinical assessment; ++: excluding extensive small cell lung cancer; §§: contamination: CT scan for screening purposes *via* the general practitioner; ƒƒ: mean years; ###: positive and indeterminate nodules; ¶¶¶: of 7582 patients in all three rounds; +++: excluding seven metastatic disease; results unknown for seven other patients who were treated by other specialists; §§: representing 72 cancers in 70 patients; ƒƒƒ: including one typical carcinoid; ####: of all cases, including positive screening in baseline; 17.6% of the participants with negative baseline screening; ¶¶¶¶: of all cases, including positive screening in baseline; 6.6% of the participants with negative baseline screening; ++++: including positive tests with incomplete information on diagnostic follow-up; §§§§: of positive tests; ƒƒƒƒ: of all positive cases with known stage; #####: percentage of the intention-to-screen groups; ¶¶¶¶¶: at least one CT.

the specificity of low-dose CT programmes. More studies are needed in order to specify and validate the role of these biomarkers to evaluate their predictive power and clinical benefit.

Screening biases

We saw earlier that, as attested by the NLST, mortality rate reduction lowered lead- and length-time biases, including the extreme aspect of length-time bias, the overdiagnosis. These biases were not overcome by other, smaller randomised controlled trials, where no mortality reduction was demonstrated. The exact impact of mortality reduction in diminishing the effect of those biases is yet to be gauged. In any case, a benefit produced for a specific population is not synonymous with a benefit enjoyed by the individual patient. It is essential that the system be able to identify those patients in whom indolent cancer may never develop to cause them real harm thus rendering treatment unnecessary. Screening, especially with a tool as sensitive as CT, identifies small lesions of uncertain significance. All lung cancer screening trials with low-dose CT found suspected nodules in a quarter to a third of examinations on average. As mentioned above, at least 90% of CT findings in most trials were false-positive results. However, even in cases of cancer diagnosis, death is not inevitable. While highly aggressive cancer will cause death regardless of screening, some very indolent cancers, particularly in older patients with co-morbidities, will not necessarily be the cause of death. Treatment of indolent cancers could end up in complications and mortality. Conversely, treatment of indolent lung cancers biases the reported results in such a way as to show higher survival rates and lower death rates of lung cancer in the screened population. Adenocarcinoma lung cancer has a wide spectrum of aggressiveness. The most indolent types progress over many years, and some will never become life-threatening cancers. In the low-dose CT screening trials, adenocarcinoma and the formerly classified BAC was the most frequent histology, found in 43% to 85% in the main randomised controlled trials [30, 32, 37, 39, 41, 45]. In 2011, a new classification of lung adenocarcinoma was issued [50]. The term "bronchioloalveolar carcinoma" (BAC) was replaced by five categories of adenocarcinoma. A new pre-invasive lesion, in addition to the existing atypical adenomatous hyperplasia (AAH), the adenocarcinoma *in situ* (AIS), was defined. The other four categories are: minimally invasive adenocarcinoma (MIA), lepidic predominant adenocarcinoma, predominantly invasive adenocarcinoma and invasive mucinous adenocarcinoma. A MIA is defined as a small solitary adenocarcinoma ($\leqslant$3 cm), with a predominantly lepidic pattern and 5 mm invasion in greatest dimension in any one focus. The AIS and MIA are rarely mucinous, and 100% or near 100% 5-year disease-specific survival is expected if the lesion is completely resected [51]. The new classification is based on a multidisciplinary approach that incorporates clinical, molecular, radiological and surgical issues. The new guidelines call for a change of terminology in describing lung lesions on CT. It is of great importance that a correlation be constituted between the histology type and radiographic imaging on CT, on the one hand, and clinical outcomes on the other. Thin-section CT appearance of sub-solid nodules can guide clinical management [52]. However, although some histological types, such as AAH or AIS, can be well correlated to predominantly pure ground-glass nodule (GGN), there is some overlap of radiological findings with histology types. More studies are required in order to enhance the correlation of radiology findings to histology, especially in view of the adaptations that the new classification of lung adenocarcinoma had necessitated.

The Fleischner Society has recently published guidelines for the management of sub-solid pulmonary nodules, which, if malignant, would mostly be correlated with the adenocarcinoma histology [53]. Since adenocarcinoma is not often predicted by risk factors such as smoking history, age and sex, all risk factors of lung cancer have the same GGN management. Recommendations are for follow-up according to lesion size ($\leqslant$5 mm or above), and a minimum period of 3 years. Multiple GGNs have also been addressed.

In order to avoid overdiagnosis, some researchers proposed measuring volume doubling time (VDT) as a marker of aggressiveness [31, 34, 54, 55]. A retrospective analysis of the VDT was made in 175 lung cancer patients in the ongoing COSMOS study (Continuous Observation of Smoking Subjects) [54]. Tumour VDT was divided into three progression categories: fast-growing ($<$400 days), slow-growing (between 400 and 599 days), or indolent ($\geqslant$600 days). Median VDT was significantly lower in new cancer compared to slow-growing and indolent cancers (52, 223 and 545 days, respectively). Significantly longer median VDT (of 303 days) was observed in adenocarcinoma with respect to squamous cell carcinoma (77 days) and small cell cancer (70 days). A similar VDT analysis was made in 63 NSCLC patients of the Pittsburgh Lung Screening Study [25], but with a different classification. Here VDT was divided into rapid ($<$183 days), typical (between 183 and 365 days), and slow ($>$365 days) [55]. Of the slow-growing tumours, 86.7% were adenocarcinoma and BAC, while squamous cell carcinoma (SCC) comprised most of the rapid-growing tumours (60%). As in the COSMOS study, tumours detected in the incidence screening were less slow-growing. Adenocarcinoma and BAC had a longer median VDT (387 days) *versus* SCC (160 days). In a recent review by INFANTE *et. al.* [56], and the corresponding editorial by REVEL [57], the slow-growing lung cancer is extensively discussed. A high VDT value of more than 400 days is one of the methods used to

 DOI: 10.1183/09031936.00164513

characterise slow-growing tumours, a method that could effect a reduction of the proportion of false-positive results rate and overdiagnosis, as so clearly demonstrated by the NELSON trial [48]. Notwithstanding this reasonable advantage of VDT in characterising tumour biology behaviour, larger studies and longer follow-up time are needed before VDT can be evaluated and made into a reliable tool.

Procedural complications of screening

Early diagnosis of NSCLC has become a prominent figure in the field of thoracic surgery. The availability of CT scanners has increased the incidence of solitary pulmonary nodule (SPN) findings as well as the use of thoracoscopy [58]. As mentioned above, changes in adenocarcinoma classification, with the new definitions of pre-invasive lesion, AIS, and MIA, may have been responsible for the 100%, or near 100%, 5-year survival after resection. Screening for lung cancer by low-dose CT, with its better performance in detecting slow-growing lung cancer, is a new challenge for surgical procedures, especially in regard to patients with multiple synchronous or metachronous lesions. This challenge coincides with fundamental changes in the field of thoracic surgery.

Once the need of diagnostic procedure is established, the most prominent procedures for SPN other than pure GGN are percutaneous CT-guided cytologic or biopsy procedure, and thoracoscopy. The complication rate of these procedures is well documented, yet little is known of complications that may arise in connection with cases of asymptomatic accidental or screening yield nodules. Indeed, this special category group may be regarded as healthier overall. Nevertheless, because lesions in this group are often too small to access, the nodules cannot be resected or sampled, a restriction which may well be a contributing factor in an increased rate of procedure failure.

The once accepted approach of muscle sparing postero-lateral thoracotomy has now been abandoned in most surgical cases in favour of video-assisted thoracoscopic surgery (VATS). Thoracoscopic procedures have evolved much in the 100 years or so since it was first reported, in 1910, by JACOBAEUS [59]. The VATS approach allows the surgeon to achieve both lobectomy and wedge resection with an equivalent or better clinical outcome than the open thoracotomy approach [60]. This minimally invasive approach, which was still controversial some 20 years ago, is now widely accepted [61, 62]. Complications of thoracoscopic procedures include prolonged air leak, bleeding, pain and wound infection. Failure to localise the nodule during the procedure may lead to conversion (expanding the surgical incision to open thoracotomy) or incompletion of the procedure. Some authors report conversion, but that may only be warranted when strong suspicion of malignancy is present. Morbidity, namely post-operative pain (post-thoracotomy syndrome) and infections, is significantly lower with the use of VATS compared to open thoracotomy surgery. The chronic sequel is typically due to post-operative pain [63], which may be controlled with adequate analgesics [64]. Anaesthesiology too has much improved over the years, and a one-time lung ventilation, with or without carbon dioxide, has proved safe [65, 66], contributing further to the lower operative risk. In the circumstances, then, the referring physician should expect achievement of the diagnosis without major adverse events, while the patient would often be able to resume full activity, including treatment regime if needed, within a few weeks after the procedure. When diagnosis has been achieved, surgical treatment may vary, depending on the type of disease and the patient's physical status.

In 1993, KAISER and BAVARIA [67] published a 10% complication rate following 106 pulmonary nodules excision. 2 years later, KRASNA *et al.* [68] reported a complication rate of 4% in 321 thoracoscopic procedures for all causes (121 for SPN diagnosis). In 1999, SWANSON *et al.* [69] published the findings of a series of 65 patients with neither major complications nor failure. A review of the literature (table 4) shows a low and decreasing rate of complications of thoracoscopic surgery from the early 1990s onwards. In the majority of publications, mortality rate is 0 (with one exception) and rate of complications range between 0 and 12%.

The treatment of choice for early-stage lung carcinoma is anatomical lobar resection accompanied with regional lymph node dissection. Sublobar resection for lung parenchyma reservation could be achieved by anatomical segmentectomy (complete resection of segment with associated nodes) or wedge resection (non-anatomical excision of the nodule with free margins). This approach could be considered in patients with more than one lesion in different lobes or patients with low cardiopulmonary reserve. The growing prevalence of early-stage lung cancer may allow sublobar resection in selected patients [74, 75]. MILLER *et al.* [76] reported a higher rate of recurrence in patients undergoing wedge resection compared to anatomical resection (lobectomy or segmentectomy) even for sub-centimetre lesions. Other authors advocated thoracoscopic surgery and sublobar resection (segmentectomy) for patients with a lesion $\leqslant 2$ cm with no differences in survival [77]. A meta-analysis showed that for patients over 71 years old wedge resection is equivalent in terms of survival to lobectomy; thus, thoracoscopic wedge resection, which has a lesser

TABLE 4 Selected study reports demonstrating the safety and efficacy of diagnostic thoracoscopy, 1992–2013

Author	Procedures n	SPN n	Failure	Complications %	Mortality
Lewis [70], 1992	100	47	3	10	0
Landreneau [71], 1992[#]	61	NR	0	12	1
Mack [72], 1992	70	21	2	0	0
Kaiser [67], 1993	266	106	NR	10	0
Krasna [68], 1995[¶]	26	NR	NA	4	0
Swanson [69], 1999	65	NR	0	0	0
Parida [73], 2013[+]	37	NR	1	0	0

SPN: solitary pulmonary lesion; NR: not reported; NA: not applicable. [#]: 43% benign lesions; [¶]: lung biopsy for interstitial lung disease; [+]: paediatric patients.

morbidity rate, may be considered for this subgroup of patients [75]. The tumour stage, VDT, patient's history and preferences will all determine the extent of the resection and the procedure chosen [56].

Table 5 summarises the lung cancer screening-related (both diagnostic and definitive procedures) complications and mortality rate as reported by the major trials. In the NLST, 60-day all-cause mortality was 0.03% (26 of 8545) of all diagnostic procedures (including clinical evaluation) in which complete data were available [41, 42] However, this figure reflects mainly (87%) noninvasive procedures (clinical evaluation and radiological studies only). Of the invasive diagnostic procedures, 60-day all-cause mortality was 2% (26 of the 1292). The 60-day mortality rates after surgical procedures (thoracotomy, thoracoscopy and mediastinoscopy) were 1% (seven of 673) and 1.7% (four of 234) in the low-dose CT and radiography group respectively, a total of 1.2% (11 of 907).

In the NLST, a low rate was also noted in the category of at least one complication, with 1.4% in the low-dose CT group and 1.6% in the radiography group. The rate for major complications after invasive procedures was low in the non-lung cancer final diagnosis (0.06% and 0.02% in the low-dose CT and chest radiography groups, respectively) and high in the lung cancer final diagnosis (11.2% and 8.2% in the low-dose CT and chest radiography groups, respectively) groups. The latter may represent the lower health status of the lung cancer patients or the presence of highly suspected lesions that resulted in aggressive evaluation and treatment. Invasive diagnostic procedures were performed in 1292 patients, of which 293 underwent thoracotomy and 104 thoracoscopy. In the thoracotomy group, 80% had lung cancer compared with 44% in the thoracoscopic group. This difference may suggest that the thoracotomies were definitive rather than diagnostic, which impacts on the mortality and complication rate.

In the NELSON trial, thoracotomy was the most common surgical procedure: 187 patients compared with 16 who underwent minimal invasive procedure [78]. Following thoracotomy, 47% (88 of 187) had minor complications and 10% (18 of 187) had major ones. Following VATS, 38% (six of 16) had minor complications, but none of these surgeries had major complications. 17% (three of 18) of major complications and 21% (20 of 96) of minor complications were observed in subjects who underwent surgery for benign disease. There was no 30-day post-operative mortality for both thoracotomy and VATS.

In two smaller trials, post-operative mortality was higher, probably due to the smaller population. In the DLCST [31], 11 patients were surgically treated, of which eight (72%) were treated by thoracoscopy. Of the three thoracotomies, there was one death on day 34 after surgery. No other complications were reported. In the DANTE trial [30, 79], post-operative complications occurred in 28 cases of the 108 (25.9%) surgical procedures, and four patients (3.7%) died postoperatively.

The field of thoracic surgery is expected to continue integrating the latest developments in lung cancer pathological restaging and imaging. The availability of safe and minimally invasive procedures allows the physician to achieve diagnosis and treatment with minimal adverse cost to the patient. It is reasonable to believe that with this general advancement and the widening access to VATS, many more medical centres will see improved results (closer to the NLST results), while complication rates decrease along the learning curve.

Radiation-related cancer risks

When ionising radiation from X-rays to the organic tissue break the binding energy of the electrons orbiting atoms and molecules, hydroxyl radicals are created that can interact with nearby DNA, or ionise DNA directly, and cause strand breaks or base damage [80]. However, development of radiation-related malignancy can happen as late as decades after exposure, which renders research in this field difficult. It is to

DOI: 10.1183/09031936.00164513

TABLE 5 Invasive procedures and surgical complications by major trials of lung screening by low-dose computed tomography (LDCT)

Trial	Participants enrolled LDCT/control	Participants who underwent invasive procedure[#] LDCT/control	Surgery LDCT/control	Mortality LDCT/control	Surgical complications LDCT/control
IELCAP [19]	1000[#,¶]	27	25	0	NR
PLuSS [25]	3755[#]	NR	82	NR	NR
DANTE [29, 30]	1403/1196	134/54	77/31[+]	3/1	22/6
DLCST [31, 32]	2052/2052	25/NR	11/NR	1/NR	0/NR
NELSON [34, 47]	7915 /7907	237/NR	215/NR	0/NR	112[§]/NR
NLST [41, 42]	26722/26732	926/366	297/121	16/10	165/59[f]
MILD [45]	1190 and 1186[##]/1723	NR[¶¶]	19/26/NR	0/0/NR	NR

NR: not reported. [#]: single arm; [¶]: including surgery; [+]: 92 surgeries reported in the original work and 108 at the review on surgical outcome [57]; [§]: 94 minor and 18 major complications; [f]: invasive non-surgical complications; 19 and six in the LDCT and chest radiography groups, respectively; [##]: biannual CT; [¶¶]: minor invasive procedures not specified.

the atom bomb survivors' analysis that we owe most of our modern knowledge of radiation-induced malignancy. A recent report of working place related exposure to prolonged low-dose radiation, documented similar findings [81]. The risk of radiation-induced lung cancer increases concomitantly with a higher baseline risk, such as in smokers, females, current compared to past smokers, long life expectancy and other parameters [82].

It has been estimated that about 1.5–2% of all cancers in the USA may be attributable to radiation from CT studies [80]. Although the risk of radiation-related cancer for any single person from a single test is small, the increasing exposure to radiation in the general population raises a significant public health issue, years after the actual exposure [80]. The effective radiation dose of chest CT can be as high as 9 mSv, but where new low-dose protocols and multi-detector scanners are being used for screening, the radiation dose is down to 0.5–1.5 mSv [43, 83, 84]. In comparison, radiation from postero-anterior and lateral chest radiography is 0.1 mSv and that of abdominal CT is 8 mSv [84]. BRENNER [82] calculated an estimate of one case of radiation-induced lung cancer for every 1000 patients at risk in the US population of 50–75 year olds undergoing annual CT screening. This represents an increase of 1.8% of the total lung cancer cases. However, calculation was based on an average effective radiation dose of 5.2 mSv, which is much higher than the current radiation dose in low-dose CT [83]. Hence, future low-dose lung CT screening can be expected to cause considerably less radiation-related malignancy. With non-lung cancer, the increased risk by radiation is estimated to be at least an order of magnitude lower [82].

Psycho-emotional effects of false-positive screening

Most nodules found in the course of screening procedures are benign and are accordingly managed with prolonged radiographical follow-up. For the patient, that constitutes what is often a lengthy and scarring ordeal before clear-up is pronounced. Most patients with pulmonary nodules assume that they have cancer and thus suffer both fear of chemotherapy side-effects and fear of death; however, there seems to be little if any association between the actual cancer risk and the patient's qualitative perception [85].

In the NELSON trial [35], the impact of lung screening processes on patients' perception of quality of life and its psychological effects were studied after the first screening tomography (and before radiographic follow-up, if needed). Comparison of different scores was performed between the negative ''normal'' result group and the indeterminate result group that required radiographic follow-up [47]. At this stage, quality of life (as represented by the 12-item short form, the EuroQol questionnaire and the visual analogue scale), and generalised anxiety scores (as represented by the Spielberger State-Trait Anxiety Inventory, STAI-6) were statistically significantly worse in the indeterminate group compared to the negative screening group, but were not clinically meaningful. Meanwhile, the lung cancer-specific distress score (represented by the Impact of Event Scale) was statistically and clinically worse in the indeterminate result group compared to the negative result group or compared to its values before randomisation. Similar assessment of the psychological effects in false-positive mammography patients had also revealed a slightly higher level of anxiety and distress, especially in the breast cancer specific related scales [86]. Reports on major psychological consequences of screening are sparse, but we note that there were two reported cases of suicide secondary to preliminary positive mammography [87].

One can hope that the increase in disease-related stress leads to better understanding and a more active involvement of individuals in the maintenance of their good health. Instances of disease-related stress can often serve as a ''teachable moment'', to encourage smoking cessation and further the reduction of other cancer risks [88]. That said, long-term follow-up did not establish a connection between lung cancer screening or false-positive results and smoking cessation [89].

Ongoing trials

Further follow-up data of participants in the randomised controlled trials are essential for better understanding of the benefits and harms of the low-dose CT screening programmes. Mortality data concerning the subjects enrolled in the ITALUNG study are first expected in 2014. By 2016, a decade after randomisation (ended December 2006), interesting mortality results are awaited of the large NELSON trial [35] and of the merging with the DLCST results [31, 32].

Based on the NELSON primary results [35], a large randomised controlled trial, the UK Lung Screen (UKLS) [90], was initiated. A pilot study, randomising 4000 participants for a single low-dose CT screening *versus* the usual care, was initiated during 2011. A further 28 000 participants will be randomised for the full trial, in which participants will be followed up for 10 years. The UKLS participants will be selected based on the risk criteria that were developed by the Liverpool Lung Project (LLP) [91]. LLP is a complex method of calculating the absolute risk of lung cancer over a defined period of time, based on age, sex, smoking duration, family history of lung cancer, history of non-pulmonary malignant tumour, history of pneumonia, and occupational exposure to asbestos. Participants eligible for the UKLS attain at least 5% LLP lung cancer risk over a 5-year period.

Guidelines for lung cancer screening

Since early 2012, guidelines for lung cancer screening by low-dose CT have been produced by various organisations (table 6). In February 2012, the Lung Cancer Screening Panel of the National Comprehensive Cancer Network (NCCN) recommended annual low-dose CT screening of all high-risk individuals at the ages of 55–74 years [92]. High-risk individuals are defined according to the inclusion criteria of the NLST (category 1: ''based upon high-level evidence, there is uniform NCCN consensus that intervention is appropriate''). However, the NCCN guidelines expanded the NLST criteria to include non-randomised studies and observational data (category 2B: ''based upon lower-level evidence, there is NCCN consensus that intervention is appropriate''). Individuals 50 years of age or older with tobacco smoking history of $\geqslant$20 pack-years and one additional risk factor of cancer history, lung disease history (chronic obstructive pulmonary disease or pulmonary fibrosis), family history of lung cancer, radon exposure, and occupational exposure should also be annually screened. Screening moderate and low-risk individuals is currently not advised. Due to weak or inconsistent evidence, screening is not advised for individuals with exposure to second-hand smoke.

The American Lung Association published, in April 2012, online guidance on lung cancer screening [93]. Recommendations for screening by low-dose CT are in accordance with the NLST eligible criteria.

A collaborative initiative of the American Cancer Society (ACS), the American College of Chest Physicians (ACCP), the American Society of Clinical Oncology (ASCO) and the NCCN published, in May 2012, a review of low-dose CT screening for lung cancer together with clinical practice guideline [94]. After first discussing the potential risks and advantages of low-dose CT screening, the authors adopt for their recommendations the NLST eligible criteria, the only randomised controlled trial that demonstrated the benefits of annual low-dose CT screening in respect of mortality from lung cancer (grade of recommendation 2B: weak recommendation, moderate quality). They do make the comment, however, that the value of the most effective duration and frequency of screening remain undetermined. Screening of patients who do not meet the NLST eligible criteria is not recommended (grade of recommendation 2C: weak recommendation, low quality). According to ASCO, the clinical practice guideline was developed from input made by the American Thoracic Society, which also endorsed this guideline [101].

In June 2012, new guidelines for lung cancer screening were issued by the American Association for Thoracic Surgery (AATS) [95]. The recommendation was based primarily on the NLST as level 1 evidence (data from a well-designed randomised control trial), but the criteria for screening was expanded. The AATS do not restrict screening to ''patients who quit smoking in the past 15 years'', since paramount risk factors are the amount of tobacco exposure and age. Since the risk of lung cancer does not decrease after 3 years of screening, the AATS recommend persisting with the performance of annual low-dose CT screening for high-risk patients from the age of 55–79 years. Age-specific incidence of lung cancer in American males increases linearly, peaking between the ages of 71–75 years. The rate of lung cancer in males and females above the age of 75 is higher than at 66–70 years of age. Coupled with the high life expectancy,

 DOI: 10.1183/09031936.00164513

TABLE 6 Eligible criteria for lung cancer early detection by low-dose computed tomography, according to guidelines or recommendations issued in 2012–2013 by different organisations

Guidelines by organisation	Date	Age years	Smoking history	Smoking cessation	Category/level[#]
NCCN [92]	Feb 2012	55–74	⩾30 pack-years	<15 years	1
		⩾50	Any and one risk factor[¶]		2B
ALA [93]	Apr 2012	55–74	⩾30 pack-years	<15 years	NA
Collaborative work of ACCP, ASCO, NCCN [94]	May 2012	55–74	⩾30 pack-years	<15 years	2B
AATS [95]	June 2012	55–79	⩾30 pack-years	Any active or former smoker	1
		50–79	⩾20 pack-years and added risk ⩾5% of developing lung cancer within 5 years[+]		2
		Any	Any and ⩾4 years remission after bronchogenic carcinoma		3
ACS [96]	Jan 2013	55–74	⩾30 pack-years	<15 years	NA
French taskforce: IFCT, GOLF [97]	March 2013	55–74	⩾30 pack-years	<15 years	NA
ACCP [98, 99]	May 2013	55–74	⩾30 pack-years	<15 years	2B
USPSTF [100]	July 2013	55–79	⩾30 pack-years	<15 years	B

NCCN: National Comprehensive Cancer Network; ALA: American Lung Association; ACCP: American College of Chest Physicians; ASCO: American Society of Clinical Oncology; AATS: American Association for Thoracic Surgery; ACS: American Cancer Society; IFCT: Intergroupe Francophone de Cancérologie Thoracique; GOLF: Groupe d'Oncologie de Langue Française; USPSTF: US Preventive Services Task Force; NA: not applicable. [#]: refer to text; [¶]: radon exposure, occupational exposure (silica, cadmium, asbestos, arsenic, beryllium, chromium, diesel fumes, and nickel), cancer history (survivors of lung cancer, lymphomas, cancers of the head and neck, or smoking-related cancers), family history of lung cancer, disease history (chronic obstructive pulmonary disease or pulmonary fibrosis); [+]: such as chronic obstructive pulmonary disease with forced expiratory volume in 1 s of ⩽70% of predicted, environmental or occupational exposures, any prior cancer or thoracic radiation, genetic or family history.

there is good reason, according to the AATS, to extend screening by low-dose CT to the age of 79 years. Furthermore, screening is also advised for patients 50–79 years of age with a 20 pack-year smoking history or other factors that produce a cumulative ⩾5% risk of developing lung cancer over the following 5 years, as level 2 evidence (data from case–control or non-randomised trials). Patients treated for primary bronchogenic carcinoma who have completed 4 years of radiographic surveillance without evidence for recurrence should also be screened, as level 3 evidence (AATS consensus opinion).

In January 2013, the ACS published its own guidelines, with recommendations for annual lung screening by low-dose CT based on the NLST eligible criteria [96]. The recommendations call for annual screening to be continued until the age of 74 years. The patient must be made fully aware of the risks and benefits involved in screening before the process begins. The programme itself must be set in an institution with expertise in low-dose CT screening, and access to a multidisciplinary team, or in centres that perform a reasonably high volume of lung CT scans, diagnostic tests and lung cancer surgeries.

A multi-disciplinary statement by French experts on behalf of the French intergroup for thoracic oncology, the *Intergroupe Francophone de Cancérologie Thoracique*, and the French-speaking oncology group, the *Groupe d'Oncologie de Langue Française*, was published in March 2013 (online in November 2012) [97]. Lung screening by low-dose CT is recommended according to the NLST eligible criteria, to be administered yearly until the age of 74 years. Subjects who consider screening by low-dose CT should be informed of the potential benefits and risks involved and agree to repeated scans or additional investigations if needed. Active smokers should consider getting advice to help them quit smoking. Algorithms for solid and sub-solid nodule management are also discussed.

In May 2013, the ACCP published its third edition of guidelines for diagnosis and management of lung cancer, including a recommendation concerning lung cancer screening [98, 99]. Annual screening *via* low-dose CT for individuals who meet the NLST eligible criteria is recommended (grade 2B: weak recommendation, moderate level of evidence), but only in settings that can deliver the same level of comprehensive care provided to NLST participants. However, knowledge is still lacking as to what would constitute the most effective duration or frequency of screening. Screening for persons who do not meet the NLST criteria is not advised.

In July 2013, the US Preventive Services Task Force (USPSTF) published a draft recommendation statement with grade B recommendation (''There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial''), for low-dose CT lung cancer screening [100].

Based on a systematic review to update the 2004 recommendation[102], the USPSTF draft recommendation states that ''a reasonable balance of benefits and harms is obtained by screening healthy persons with a 30 pack-year or more history of smoking who are ages 55 to 79 years and have smoked within the past 15 years. Caution should be used in recommending screening to patients with significant co-morbidity, particularly those who are toward the upper end of the screening age range''. The number of years needed for screening is not specified, but based on modelling studies conducted for the USPSTF by the Cancer Intervention and Surveillance Modeling Network (CISNET), age range is extended up to 79 years instead of the NLST 74-year limit [100].

To summarise, all of the above guidelines recommend considering screening programmes for individuals who meet the eligible criteria and are medically fit for further evaluations. Discussing the potential benefits and harms of low-dose CT screening with the patient is mandatory. Screening programmes should take place in centres that are operated by multidisciplinary team of physicians skilled in low-dose CT screening, positive lesions evaluation and treatments. The different guidelines are also in agreement in their rejection of the chest radiography and sputum cytology option for lung cancer screening, and they all favour coupling the screening with smoking secession programmes.

In summary

Screening for lung cancer has repeatedly disappointed the hopes of achieving better effectiveness. Sputum cytology and chest radiography failed to reduce lung cancer mortality. Using low-dose CT for screening increased detection of lung cancer in early stages of the disease, yet mortality reduction was not demonstrated by some small randomised controlled trials. Stage shift was not marked in both the smaller and large randomised controlled trials. In October 2010, a large randomised controlled trial, the NLST [41], in which more than 53 000 participants were randomised into two arms, a 3-year screening programme of annual low-dose CT *versus* chest radiography was terminated ahead of schedule, due to significant reduction in mortality in favour of low-dose CT screening. Overall mortality, including death from lung cancer, was relatively reduced by 6.7% and 20%, respectively, in the low-dose CT group, as compared with the radiography group. In order to prevent one death from lung cancer, 320 participants needed to be screened at least once. Lung cancer was diagnosed in 63% of the patients screened with positive results. Yet, stage shift was not demonstrated, since the rate of advanced stages (IIB–IV) was not significantly different between the CT and the chest radiography groups.

Based on the NLST results, new guidelines were developed by various organisations (table 3). All recommend considering annual screening for lung cancer by low-dose CT for persons between the ages of 55 and 74 years, with some guidelines extending the criteria for patients up to the age of 79 years (AATS and USPSTF), or starting from the age of 50 years if other risk factors for lung cancer exist (NCCN, AATS). The AATS also dropped the criteria of quitting smoking in the past 15 years for ex-smokers. It is further established that randomised controlled trials of screening for lung cancer by chest radiography lack efficacy and should therefore be avoided.

Screening by low-dose CT is not free of negative effects. Exposure to ionised radiation annually is still a concern, especially in high-risk patients. Since suspicious findings are found in up to 30% of the participants in randomised controlled trials, in which more than 90% are benign (table 2), noninvasive and invasive procedures need to be performed solely as a consequence of the screening. Disease-specific distress is more prevalent among patients mandated for further evaluation by the screening protocol. Complications of invasive procedures are more likely to happen in patients in whom lung cancer is confirmed. Highly suspicious lesions require more aggressive evaluation and treatment. It is expected, though, that the evolving field of thoracoscopic surgeries will minimise the occurrence of major complications and mortality.

Extending screening to the general population in all medical centres is riddled with uncertainties. Most of the randomised controlled trials to date were conducted in large medical establishments, where CT interpretation was made by a well-trained radiologist and re-evaluated by more than one in case of doubt. Positive lesions were evaluated in tertiary hospitals with well-trained specialists. Another factor to consider is the fact that selection of patients may well have biased the evaluation results. In the NLST, participants were younger, better educated, and less likely to be current smokers in relation to the general US population that meets the major NLST eligibility criteria [103]. It is therefore questionable whether expanding screening to the general population in medical centres with different experience will produce the same balance of advantages and complications as existed in the NLST. It is likely that with the new guidelines in place, many more medical centres will acquire expertise, which will eventually lead to better performance of

 DOI: 10.1183/09031936.00164513

all relevant professions and better evaluation protocols. It will be of great significance to have data systematically collected from all screening programmes and supervised at the national level. Information from ''real-life'' experience should be re-examined and recommendations evaluated accordantly.

In light of the many pitfalls of lung cancer screening, it is essential that the programme be offered to patients who are able to go through further evaluation both physically and emotionally and with relatively high compliance. A pre-screening discussion with the patient is deemed mandatory, so that the patient is aware of the potential advantages and harms involved. For the programme to be effective and beneficial, it needs to be operated in medical centres where multidisciplinary teams specialised in CT screening are at hand. Participants ought to be made aware that lung cancer screening is not a substitute for smoking cessation and should be encouraged to quit smoking and offered a suitable programme to help them with the process.

Cost-effectiveness calculation of low-dose CT screening is highly involved. According to the NLST, there are about 7 million persons in the US who qualify for the screening criteria. Beyond the cost of the low-dose CT, the cost of further follow-up and evaluation in case of positive findings such as PET-CT, biopsies and surgical interventions, as well as emotional distress and loss of working days need to be measured. According to a recent analysis by the Research and Economic Assessment of Cancer and Healthcare (REACH), low-dose CT screening will add $1.3–2.0 billion in annual national healthcare expenditure for screening uptake rates of 50–75%, respectively [104]. It is estimated that at a 75% screening rate, low-dose CT screening will prevent up to 8100 premature lung cancer deaths. The additional cost of screening to avoid one lung cancer death is $240 000.

In future, more work needs to be done towards establishing the optimal acceptance criteria for patients, which will make screening by low-dose CT more beneficial. Risk models should be improved to better define high-risk patients. With more accurate evaluation of comorbidity and life expectancy, such models would also help in cutting down the number of unnecessary screenings. Nevertheless, new types of non-surgical effective treatments, such as stereotactic body radiation therapy, and local thermal tissue destruction, such as radio-frequency ablation or biological treatments, are constantly developing and could be offered to selected high-risk patients. At the same time, new possibilities of creating new tools that will increase the outcome prediction capability should be explored, including biomarkers, identifying new risk factors, and better correlating the radiology appearance with the pathology. Such tools will help deal more effectively with cases of adenocarcinoma in its new classification, the most prevalent lung cancer, especially among nonsmokers, females, and other patients who do not meet the NLST criteria. Classifying nodules according to risk, namely benign, slow-growing and aggressive cancers, could better guide further evaluation, and more accurate protocols should be developed in each case.

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DOI: 10.1183/09031936.00164513