REVIEW ARTICLE

Screening for lung cancer with low-dose computed tomography: a review of current status

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ABSTRACT Screening using low-dose computed tomography (CT) represents an exciting new development in the struggle to improve outcomes for people with lung cancer. Randomised controlled evidence demonstrating a 20% relative lung cancer mortality benefit has led to endorsement of screening by several expert bodies in the US and funding by healthcare providers. Despite this pivotal result, many questions remain regarding technical and logistical aspects of screening, cost-effectiveness and generalizability to other settings. This review discusses the rationale behind screening, the results of on-going trials, potential harms of screening and current knowledge gaps.

KEY WORDS Lung neoplasms/mortality; mass screening tomography; helical computed; early detection of cancer/methods

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Introduction

The rationale for lung cancer screening

Lung cancer caused an estimated 1.4 million deaths in 2008 (1), and is the leading cause of cancer death worldwide. Incidence and mortality closely follow smoking trends with a time-lag of twenty years. This explains why death rates are falling or plateauing in countries such as the US, yet rising in others such as China (2,3). Lung cancer carries a poor prognosis with reported overall five year survival between 8 and 16% in Europe and the USA, and between 6% and 32% in China (4-6).

Currently 25-30% of patients present with localised, potentially curable disease. Five year survival for those with pathological stage IA non-small cell lung cancer (NSCLC) is 73% whereas metastatic disease has a dismal prognosis (13% 5-year survival) (7,8).

Given that lung cancer has a detectable pre-clinical phase, effective treatment, especially surgery, with effective and potentially cost-effective applicable screening methods, it would seem to fulfil the criteria for screening first described by Wilson and Jungner (9) (Box 1). Although early screening studies using plain chest radiography (CXR) had methodological drawbacks (11), it is generally accepted that CXR screening does not confer a mortality benefit, a conclusion reinforced by the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (12). In contrast, computed tomography (CT) is a far more sensitive imaging modality which has been studied for its potential utility in lung cancer screening over the past 25 years. Recently, the National Lung Screening Trial (13) showed that low-dose CT (LDCT) screening reduced lung cancer mortality by 20% compared with CXR screening. This was the first demonstration in a randomized clinical trial of a mortality reduction with screening. In response to these findings several expert bodies in the USA issued guidelines for screening high-risk populations and the US Preventive Services Task Force has awarded a Grade B draft recommendation (14-17).

LDCT screening--practical issues and technical considerations

One of the most important issues confronting those who wish to consider implementation of LDCT screening in high-risk populations is the problem of the high rate of positive examinations, primarily pulmonary nodules.

Nodule detection

Pulmonary nodules can be defined as rounded or irregular

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Box 1. Principles of early disease detection [adapted from Wilson and Jungner (9)].

Condition
- The condition should be an important health problem.
- There should be a recognisable latent or early symptomatic stage.
- The natural history of the condition, including development from latent to declared disease should be adequately understood.

Test
- There should be a suitable test or examination.
- The test should be acceptable to the population.

Treatment
- There should be an accepted treatment for patients with recognised disease.

Screening program
- There should be an agreed policy on whom to treat as patients.
- Facilities for diagnosis and treatment should be available.
- The cost of case-findings (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case-findings should be a continuing process and not a 'once and for all' project.

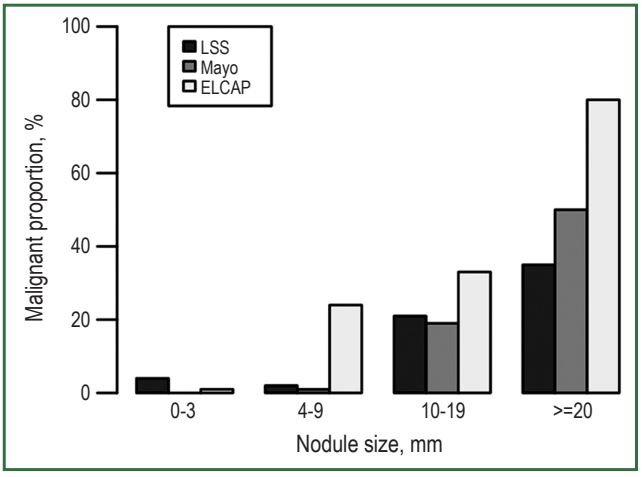

Figure 1. Nodule size correlates to risk of malignancy*. LSS, Lung Screening Study; Mayo, Mayo Clinic Study; ELCAP, Early Lung Cancer Action Project. *Cut-off sizes were slightly different between studies (29-31).

opacities, well or poorly defined, measuring up to 3 cm in diameter (18). There is inherent subjectivity in identifying nodules, reflected in inter- and intra-reader variability, even amongst experienced radiologists (19,20).

A considerable proportion of nodules may be missed at first reading and identified retrospectively at later scans (21). Nodule detection may be increased by using a second reader (22), image formatting, e.g., to maximum intensity projections (MIPs) (23-25) or by using computer aided detection (CAD) software as a "second reader" (26-28).

Nodule assessment

Nodules are best classified in four important ways: size, attenuation, presence/absence of calcification and, once a follow-up scan has been obtained, interval growth rate.

Size

Nodule size is the most important predictor for malignancy (Figure 1) (29-31). Detailed analysis of baseline NLST results found the positive predictive values (PPV) for malignancy increased significantly from 1.7% for nodules 7-10 mm in diameter to 11.9%, 29.7% and 41.3% for those 11-20, 21-30 and >30 mm diameter respectively (32). However even very small nodules (micronodules) have some risk of malignancy, e.g., 3 of 230 nodules <5 mm diameter (1.3%) at baseline scan followed for one year (33).

Attenuation

Certain calcification patterns and intra-nodular fat reliably indicate benignity (34), however, many nodules are too small to resolve internal features and are simply classified as 'non-calcified' nodules (NCNs). NCNs are common and detected in 25-50% of LDCT scans.

The majority of NCNs are of 'solid' (soft-tissue) radiological attenuation. The remainder are classified as non-solid nodules (NSNs) and subdivided into pure ground-glass (pGGO) or mixed (part-solid) attenuation nodules (solid and ground-glass components; psGGO). Synonyms vary between studies (Figure 2). The significance of GGOs is contentious as discussed below.

Ground glass opacities

The ELCAP study reported positive findings in 233/1,000 baseline scans. 19% of lesions were pGGO or psGGO (prevalence 4.4%; slice thickness 10 mm). Twenty-seven cancers were detected. After adjusting for size, the malignancy rate was 63% for psGGO, 32% for solid nodules and 13% for pGGOs (35). Other studies highlight the importance of a new or increasing solid component within NSNs, a finding highly suggestive of lung cancer (36-38). More recent studies demonstrate many NSNs spontaneously resolve. Felix (39) reported 75 GGOs in

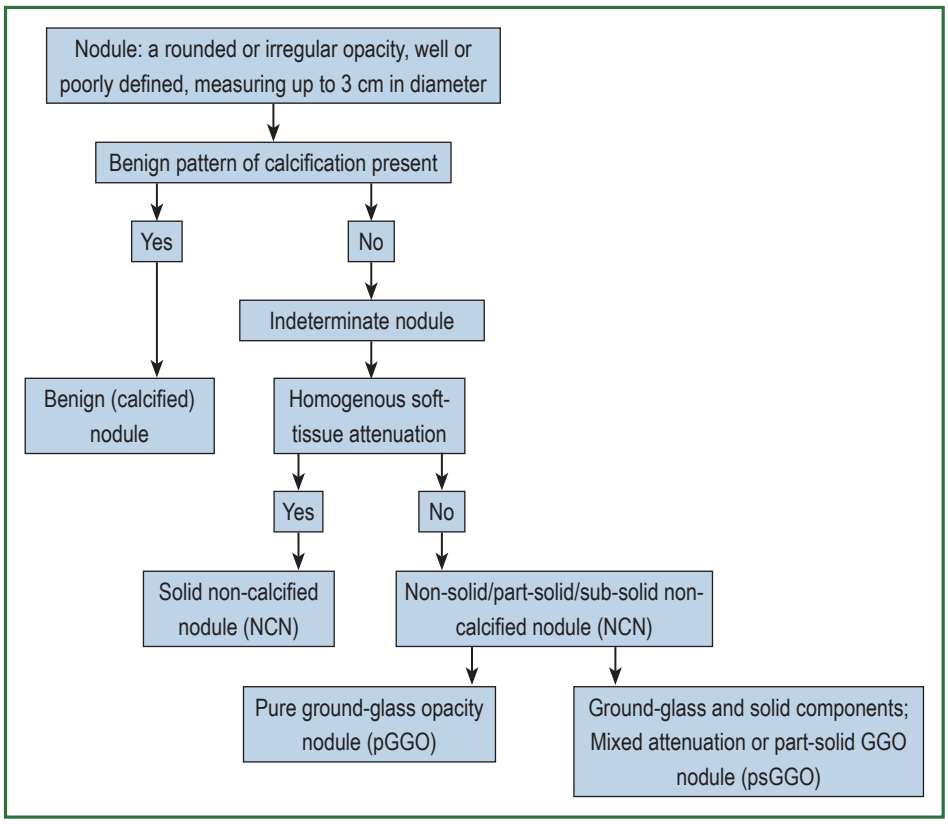

Figure 2. Classification of nodules detected by LDCT screening.

37/280 patients (prevalence 13%; slice thickness 0.75 mm). The population was atypical for screening studies as over half had a history of lung or head and neck cancer. Approximately half the GGOs were present at baseline and half disappeared over a median 29 months follow-up. No morphological features allowed reliable discrimination between resolving and non-resolving GGOs. Kwon (40) reported 69 pGGO and 117 psGGO mostly detected by screening in 186 patients (total screenees not reported; slice thickness 5 mm). After 3 months, 45% regressed or disappeared. Malignant and benign lesions were similar in size (average 15-16 mm). Only 27% (33/122) were malignant but this may reflect a short follow-up time (mean 8.6 months; 64 lesions were still under active follow-up at publication). A second Korean study (41) identified 126 NSNs >5 mm diameter in 93 of 16,777 (0.5%) asymptomatic screenees. Forty-four had never smoked. 70% of NSNs were transient. Younger age, detection at a follow-up scan, blood eosinophilia, multiple lesions, larger solid component and ill-defined border independently predicted transiency. Mario (42) reported 76 NSNs retrospectively identified in 56/1,866 baseline screening scans in a high-risk screening cohort (prevalence 3%; slice thickness 0.75 mm) and followed for 50±7.3 months. Only 13 nodules were prospectively identified. 40 of 48 pGGOs (83%) resolved, decreased in size or remained stable. 16 of 28 psGGOs (57%) resolved or remained stable. Overall, 74% NSNs resolved, decreased in size or remained stable and 26% progressed. One psGGO (2%) was confirmed as lung adenocarcinoma.

In summary, perhaps as many as 50-70% of NSNs detected on modern thin-slice CT scans are transient but predicting which will persist is currently beyond our ability. The data suggest that a substantial difference in NSN prevalence between Western and Asian populations is unlikely. In view of slower growth rates for non-solid tumours (37,43) active surveillance for >2 years may be prudent for non-resolving NSNs (44).

Growth rate

Once a follow-up scan is obtained, assessment of growth can be made. Generally, absence of growth in a solid nodule over a 2 year period makes malignancy unlikely (45), although a contemporary review found the underpinning data (based on CXR studies from the 1950s) less than compelling (46).

Growth is best assessed by CT. For example, assuming exponential growth, a 5 mm diameter nodule with a volume doubling time (VDT) of 460 days will only increase to 6 mm diameter after one year and 7.2 mm after two years-changes which may not be measurable on CXR but which can be appreciated on CT. However, reproducible measurement is difficult: the 95% confidence intervals (CIs) for inter-reader measurements of nodules with a mean diameter of 8.5 mm were +/– 1.73 mm in one study (47). Semi-automated volumetric measurement

using computer software may be more reproducible and accurate (48,49) and is the basis of nodule management in the NELSON trial (47-50). However even this is subject to error, e.g., with smaller nodules, in the presence of motion artefact (51), nodules attached to other structures and NSNs (52).

There are limited long-term data supporting the two year stability guideline for sub-centimetre NCNs; In an Irish study (53) 83 subjects with NCNs <10 mm stable over two years were imaged again at seven years. Virtually all nodules remained unchanged at the seven-year CT, however one 3 mm GGO grew to 15 mm in four years and was subsequently diagnosed as (what was previously called) bronchioloalveolar cell carcinoma. Thus ideally, the two year stability guideline suggested by CXR studies should be validated in larger, contemporary CT datasets.

The importance of baseline size and interval growth is shown in data from the NELSON study (54). 891 solid nodules 5-10 mm diameter were followed for one year. 743 nodules, all with smooth margins and/or attached to fissures, pleura, or vessels (contact length ≥50% of nodule diameter) were benign and excluded from multivariate analysis. Spiculated, irregular or lobulated nodules were analysed further. 10 of 69 (14.5%) nodules with spiculated or irregular margins and 6 of 168 (3.6%) nodules with lobulated margins were malignant. At baseline the only characteristic that predicted malignancy was volume ≥130 mm^3 (OR 6.3; 95% CI: 1.7 to 23.0). At 3-months, baseline volume and VDT <400 days were significant (OR 4.9; 95% CI: 1.2 to 20.1 and OR 15.6; 95% CI: 4.5 to 53.5, respectively); At one year only VDT was predictive (OR 213.3; 95% CI: 18.7 to 2,430.9). Very few nodules showed change in margin or shape over 12 months, so these features were unable to distinguish malignant from benign nodules (55).

Other morphological features

Diederich (56), in a study of 133 consecutive resolving nodules, found the demographic and morphologic features of resolving and non-resolving nodules overlapped so greatly that none could be used to predict outcome over two years' follow-up.

Features of benignity noted by Takashima after two years follow-up (72 nodules ≤10 mm diameter including 25 cancers) were polygonal shape, subpleural location, solid attenuation and elongation (higher long-axis-to-short-axis diameter ratio) (57). Long-term analysis of 234 similar nodules (perifissural with any of the following features: polygonal shape, long-axis-to-short-axis diameter ratio >1.78, peripheral location, vascular attachment) detected in 98/146 consecutive screenees found the nodules were multiple in half the subjects, ranged from 1-13 mm diameter, were mostly triangular or oval (86%), inferior to the carina (84%) and had a septal connection (73%) (58). 139 screenees were accounted for after 7.5 years, and none of the perifissural nodules had developed into cancers. These types of nodules most probably represent intrapulmonary lymph nodes, however histopathologic confirmation was not performed in either study (57,58).

The difficulty in predicting which nodules might be malignant is highlighted by low PPV in screening studies; with a cancer prevalence of 1-2% the PPV of a nodule designated by the radiologist as 'suspicious' or large in size or with VDT <400 days actually being malignant was only around 35% in two studies (50,59).

Nodule management protocols

LDCT nodule management protocols reflect the association of size and growth with malignancy. The protocols from the three largest studies, NLST, NELSON and I-ELCAP are summarized in Table 1 (52,60,61). These protocols have been applied to 26,722, 7,557 and 31,567 LDCT screenees respectively although I-ELCAP has no control arm. Size category definitions vary slightly, but in general terms 'micronodules' (usually less than 4-5 mm diameter) are followed after 12 months, large nodules (>10-15 mm diameter) are sent for immediate investigation and medium size nodules are followed-up to determine growth. Most studies use linear measurements of nodule size but the NELSON study uses volumetric measurement (50). Retrospective analysis of I-ELCAP data suggested the threshold to define a 'positive' baseline scan may be too inclusive; increasing the threshold to 7-8 mm (mean of maximal diameter and width) may reduce the false positive rate and subsequent work-up by 50-68% but at the cost of diagnostic delay for 5-6% of true positive cases (62). To date, only the NLST protocol has been proven to reduce lung cancer mortality.

Non-nodule (incidental) findings (IFs)

Non-cancer IFs such as coronary artery calcification (CAC), emphysema, and thyroid nodules are common but rates vary widely depending on study definitions and recording protocols. A NELSON substudy (n=1,929) found an IF rate of 81%. Six percent of participants received follow-up but only 1% had clinically important findings arguing against systematically searching for IFs (63). A Canadian study (n=4,073) found IFs in 19%; Approximately half would have required follow-up and 0.8% immediate action (64).

LDCT screening may be an opportunity to screen for other conditions which can be detected on chest CT such as CAC, chronic obstructive pulmonary disease (COPD) and osteoporosis (65,66). This may increase cost-effectiveness and provide better global outcomes but is currently untested. Radiologist-detected emphysema on CT scans appears to confer an independent increased risk of lung cancer (OR 2.1) (67) and may have the potential to help determine screening frequency following baseline scan (68) (i.e., more frequent screening for those with visually-detected emphysema), but this hypothesis remains to be tested.

CAC, a risk marker for cardiac events (69) is potentially the most important IF. Worldwide, smoking is estimated to cause

Table 1. Comparison of nodule management protocols for three leading LDCT studies.

		Nodule characteristics (attenuation, diameter, volume)	Recommended action	Interval findings	Recommended action
Small	*NLST*	<4 mm d_{max}	12 m LDCT		
	NEL	<50 mm^3 without benign characteristics			
	IE	Solid/ part-solid <5 mm d_{mean}; non-solid: any size			
Intermediate	*NLST*	Solid 4-10 mm d_{max}	3-6 m LDCT (may vary up to 24 m according to level of suspicion)	No growth[†]	→ 12 m LDCT
				Growth <7 mm	→ 3-6 m LDCT or refer to pulmonologist
				Growth ≥7 mm	→ Refer to pulmonologist
		Pure GGO 4-10 mm d_{max}	6-12 m LDCT	As per solid 4-10 mm nodules	
	NEL	Solid: 50-500 mm^3; Solid, pleural based: 5-10 mm Mixed: GGO component: ≥8 mm d_{mean} or solid component: 50-500 mm^3 Pure GGO: ≥8 mm d_{mean}	3 m LDCT	Growth[††]	→ Refer to pulmonologist
	IE	Solid/ part-solid 5-15 mm d_{mean}	3 m LDCT (preferred option) or Antibiotics & 3 m LDCT if infection possible or	Growth[†††]	→ Biopsy
			PET scan if solid/solid component >10 mm	PET scan negative	→ 3 m LDCT
Large	*NLST*	Solid >10 mm d_{max} Other suspicious finding	Refer to pulmonologist		
	NEL	Solid: >500 mm^3; Solid, pleural based: >10 mm Mixed, solid component: >500 mm^3			
	IE	Solid/ Mixed >15 mm d_{mean}			

Key: *NLST-NLST, NEL-NELSON, IE-I-ELCAP*; m, month; d_{mean}, mean of maximal diameter and width viewed on same CT slice; d_{max}, maximal diameter on axial CT slice; PET, Positron-emission tomography; GGO, ground glass opacity attenuation nodule; Definitions of growth minimum significant change: [†], >10% increase in diameter; [††], ≥25% increase in volume after at least a 3 months interval; [†††], Minimum change in nodule diameter/solid component of part-solid nodules to define significant growth: for nodules <5 mm in diameter, ≥50%; for nodules 5-9 mm in diameter ≥30%; for nodules >10 mm in diameter ≥20%. Adapted from NLST (60) NELSON (52), I-ELCAP (61).

0.8 million deaths from acute heart attacks annually (70). The ELCAP investigators found varying degrees of CAC in 64% of 4,250 screenees (71). They developed a simple visual scoring system which was able to stratify cardiovascular death risk in a second cohort of 8,782 screenees followed for a median of six years (72). The NELSON study reported higher hazard ratios for all-cause mortality with increasing CAC in 958 participants followed for 21 months (73). However these findings do not appear to be reflected in NLST data where approximately 75% of all deaths were from non-lung cancer causes (13). Cardiovascular illness accounted for 486/1,865 (26.1%) deaths in the LDCT group and 470/1,991 (23.6%) in the CXR group. The 6.7% reduction in all-cause mortality in the LDCT group lost statistical significance when lung cancer deaths were removed from the comparison (3.2%, P=0.28) indicating that reduced lung cancer mortality was largely responsible for the reduction in all-cause mortality (13). Clinically significant IFs were identified in 7.5% of all scans and although details of

Table 2. Results from selected observational LDCT lung cancer screening studies.

	Year	n	Cohort characteristics	Additional tests	Cancer prevalence %	Cancer incidence %	Stage I tumours %	5-year survival
ELCAP (31)	1992	1,000	>60 yr old; >10 PY smoking	CXR	2.7	0.6	85	65%
ALCA (74)	1993-95	1,611	40-75 yr old; 14% non-smokers; 16% <50 yr old	Sputum cytology, CXR	0.87	0.28	82	70%
Matsumoto Research Centre (75)	1996-98	5,480	40-74 yr old; 54% never smokers; 10% <50 yr old	Sputum cytology	0.41	0.23-0.56	83	83%
Mayo Clinic (76)	1999	1,520	>50 yr old; >20 PY smoking	–	1.9	2	56	–
I-ELCAP (77)	1993-2005	31,560	>40 yr old; 16% never smokers	–	1.3	0.3	85	80% (10 yr)

CAC prevalence and follow-up are not yet reported, it seems unlikely that identification of CAC on LDCT screening made a significant impact on cardiovascular mortality in this study.

Thus IFs are common but mostly of little significance. Exhaustive investigation of IFs will increase the costs of screening through downstream investigation and follow-up, and should be accounted for in cost analyses. Further analysis of CAC and possibly other conditions in screening studies is warranted.

Screening by LDCT-effectiveness

Observational studies

The earliest LDCT screening studies were observational cohort studies from the USA and Japan (Table 2). CT appeared to be 3-4 times more sensitive than CXR in the ELCAP study, and the majority of tumours were stage I. Entry criteria were varied. Studies recruiting younger participants (<50 years old) and never-smokers had lower prevalence and/or incidence rates. For example, in a Japanese study (75) in which the majority of screenees had never smoked, cancer prevalence was only 0.4% compared to ELCAP 2.7% (31). These results underline the importance of recruiting a high-risk population. Subsequently, most studies follow the ELCAP strategy recruiting older persons with extensive smoking histories. Risk stratification is an area of current research interest and is discussed later.

Although very promising, these studies lacked control groups to allow estimation of mortality benefit. Survival, as a surrogate endpoint of effectiveness, is subject to several biases and cannot therefore be used to prove screening efficacy (Box 2). To add to the debate, studies modelling mortality benefit markedly diverged in their conclusions (78-80).

Randomised controlled trials

The randomised control trials of LDCT screening are summarized in Table 3. Two trials, the NLST (USA) and NELSON (Holland/Belgium), have adequate statistical power to detect a reduction in lung cancer mortality. The smaller European studies are planning a meta-analysis (93). All European studies (except for Depiscan and DANTE) randomised LDCT screening against no screening, the current standard of care.

The most important RCT result to date is from the NLST study (13). This landmark study randomised 53,454 high risk volunteers to three rounds of screening by CXR or LDCT (baseline, year 1 and year 2) and followed up for a median of 6.5 years. Eligibility criteria included: current or former smokers with ≥30 pack year smoking history (quit no more than 15 years previously); No history of lung or other cancer in the past five years; No current symptoms suggesting lung cancer; No chest CT in the previous 18 months. The study demonstrated a relative reduction in lung cancer-specific mortality of 20.0% in the LDCT arm (95% CI: 6.8 to 26.7; P=0.004).

Despite this positive result, several issues remain particularly generalizability and cost-effectiveness. The NLST authors stated their data alone are 'insufficient' to fully inform lung-cancer screening recommendations (13) and the Position Statement from the International Association for the Study of Lung Cancer (IASLC) Task Force on CT Screening reminds us that screening benefit, costs and potential harms must be defined in a 'cultural context', i.e., positive results seen in USA studies may not translate directly to other countries or healthcare systems (94). Additionally, the negative effects of screening and knowledge gaps, discussed below, must be considered.

Screening adherence

Good adherence is important to the success of mass screening. NLST reported 95% adherence across all three screening scans and NELSON reported 97% at year two. Long-term

Box 2. Survival bias in screening studies.

Bias in screening studies

- This box describes the three most important survival biases in screening studies. Survival cannot be used as a robust endpoint as, without a control group, there is no way of determining the relative contribution of each bias. Relative mortality between the intervention (screened) and control group is the best endpoint to use.

Lead-time bias

- Survival is measured from time of diagnosis to time of death. CT is more sensitive than CXR and will therefore detect smaller tumours earlier. Even though there may be no benefit in terms of reducing mortality, survival will appear longer for CT detected tumours as the diagnosis was simply made earlier.

Length bias

- Screening tends to detect slower-growing tumours and miss more aggressive ones. Rapidly-growing and aggressive tumours are more likely to grow and metastasise in the between-scan interval, and thus be missed whereas slowly growing tumours have a longer preclinical phase and are more likely to be detected by screening. As screening selects for less aggressive tumours, outcomes are more favourable thus survival may appear better in the screened group.

Overdiagnosis bias (pseudodisease)

- The detection of tumours which are never destined to cause morbidity; the patient dies from competing causes 'with' the cancer rather than 'from' it. In the absence of screening the cancer would never have been diagnosed in the lifetime of the person. Most of these tumours will be slow-growing or indolent. People at risk of lung cancer have a high risk of dying from other causes because of the shared risk factors of smoking and older age. Overdiagnosis bias makes screening appear to be more successful than it really is but essentially has detected non-lethal disease. This is a major problem in prostate cancer screening where, for example, as many as 60% of cases detected by prostate-specific antigen screening may be overdiagnosed (10). Individuals with overdiagnosed cancer undergo investigation and treatment with no hope of living longer. This futile management exposes patients to unnecessary harms and diverts finite health resources from other areas. Overdiagnosis in lung cancer screening has yet to be quantified (see text).

observational studies report 80% adherence at year five and 86% at year seven (76, 95). How this will translate to the 'real world' is not known.

Downstream healthcare use

Positive scans and incidental findings require clinical and radiological follow-up. Healthcare use may rise in the first six months following screening but return to baseline levels 6-12 months after screening and appears independent of result (i.e., negative, indeterminate or suspicious findings) (96). Although this study found doctor visits increased by 50%, in absolute terms this only meant one extra visit per participant (96).

Cost-effectiveness

Cost-effectiveness, a fundamental requirement of screening implementation, remains to be addressed. It depends on a complex mix of factors which vary from program to program and country to country (Table 4). Estimates vary widely depending on the underlying assumptions and models used, making conclusions difficult to draw (97). Using NLST data, Goulart estimated that if 75% of the eligible US population underwent screening, the cost to avoid one lung cancer death would be $240,000 (98). McMahon's analysis paid particular attention to a model combining screening and smoking-cessation (99). The estimated cost per Quality Adjusted Life Year (QALY) in a cohort of 50 years old could be below $75,000/QALY if quit rates could be doubled from the background rate. From a health insurance perspective cost estimates were highly favourable (100); screening high-risk 50-64 years old would cost $1 per insured member per month, and the cost per life-year saved would be below $19,000.

To date, heterogeneous modelling methodologies and underlying assumptions have led to highly conflicting cost-effectiveness estimates. The final analysis from NLST has yet to be reported in a peer-reviewed format and is eagerly awaited. Preliminary data (101) suggest that it will be cost-effective with an Incremental Cost Effectiveness Ratio (ICER) of $72,900 US per QALY.

Negative effects of screening

Screening for any disease has risks and benefits. The balance helps determine overall effectiveness and acceptability of the screening program. The main negative effects are discussed below.

Radiation

It is generally accepted that ionising radiation is a cause of cancer without a lower "dose" threshold, although the absolute level of risk is debated (102,103). Minimising radiation dose according to the ALARA principle ('as low as reasonably acceptable') (104) is particularly important when screening asymptomatic, healthy subjects. CT radiation dose is determined by many factors including tube current, tube voltage, the use of filters and scan

Table 3. Randomized clinical trials of lung cancer screening using low-dose computed tomography; Target group and screening schedule.

Study	Age range	Smoking history	Participants (baseline), n			Screening schedule (years)**	Control group	Total period of follow up	Years of recruitment	Completion/ expected completion
			LDCT arm	Control arm	Total					
NLST, USA (13,81)	55-74	Current or ex-smokers >30 PY, quit <15 yr	26,722	26,732	53,454	0,1,2	CXR	5	2002-4	2009
LSS, USA (pilot study) (82)	55-74	Current or ex-smokers >30 PY, quit <10 yr	1,660	1,658	3,318	0	CXR	1	2000	2001
DANTE, Italy (83)	60-74 (men only)	Current or ex-smokers >20 PY	1,276	1,196	2,472	0,1,2,3,4	Annual clinic review†	4	2001-6	2010
Dépiscan, France (pilot study) (84)	50-75	Current or ex-smokers >15 PY, quit <15 yr	336	285	765	0,1,2,3	CXR	2	2002-4	2004
NELSON, The Netherlands and Belgium (50,85,86)	50-74	Current or ex-smokers >15 PY, quit <10 yr	7,915	7,907	15,822	0,1,3	Usual care (no intervention)	10	2003-6	2015
DLCST, Denmark (87)	50-70	Current or ex-smokers >20 PY, quit <10 yr	2,052	2,052	4,104	0,1,2,3,4	Usual care (no intervention)	10	2004-6	2014
ITALUNG, Italy (88)	55-69	Current or ex-smokers >20 PY, quit <10 yr	1,613	1,593	3,206	0,1,2,3	Usual care (no intervention)	4	2004-6	–
MILD, Italy (89)	49-75	Current or ex-smokers >20 PY, quit <10yr	1,190 annual; 1,186 biennial	1,723	4,099	Annual or biennial for 10 years	Usual care (no intervention)	10	2005-onwards	Ongoing-started 2005
LUSI, Germany (90)	50-69	Current or ex-smokers >15 PY, quit <10yr	2,029	2,023	4,052	0,1,2,3,4	Usual care (no intervention)	5	2007-onwards	Ongoing-started 2007
UKLS (pilot study), United Kingdom (91,92)	50-75	5% risk of developing lung cancer in 5 years (Liverpool Lung Project risk model)	2,000*	2,000*	4,000	0	Usual care (no intervention)	10	2011-onwards	Ongoing-started 2011

*Planned recruitment; PY, Pack years (cigarettes per day/20× duration of smoking in years); CXR, chest radiograph; **Screening schedule indicates which year the scans are performed with '0' indicating baseline scan; †, all participants received CXR + sputum cytology at baseline.

Table 4. Factors affecting screening cost-effectiveness.

Population	Screening intervention	Nodule management	Clinical
Disease prevalence in the target population (determined by risk, e.g., age, smoking history)	True-positive rate	Definition and rate of 'positive' scan results	Stage distribution of detected disease
Uptake of screening	False-positive rate	Nodule follow-up algorithm	Treatment costs
Adherence to screening	Over-diagnosis rate	Invasive diagnostic procedure rate	Investigation and treatment of incidental findings
	Screening frequency (interval between scans)	Adverse event rate	
	Screening duration (years)	Cost of diagnostic work-up	
	Lung cancer mortality reduction		
	Effectiveness of smoking cessation program		
	Radiation exposure		
	Cost of screening scan		

length (Z-axis). In screening studies, the most common way to limit dose is to adjust tube current (milliamperes, mA) (105) according to patient weight. This can degrade image quality as image noise (grainy mottling) is inversely proportional to the square root of the radiation dose. Fortunately the inherently high contrast between air-filled lung parenchyma and soft tissue lesions means pulmonary nodules are well-visualised. The mean effective dose from screening CT scans can be reduced from 8 mSv (standard CT chest) to approximately 1.5 mSv without significant deterioration in resolution or image quality (13,106,107). Although the lower radiation dose results in more noise it has been shown to provide adequate diagnostic pictures and is thus the current standard for screening (108-110). Total radiation dose can be further limited by restricting the scope of follow-up CTs to a region of interest surrounding the nodule(s) in question rather than covering the entire chest, so-called 'limited' LDCT (111).

Smoking appears to interact synergistically with ionising radiation. In absolute terms the risk of cancer from LDCT is small, perhaps only an excess lifetime risk of 0.85% (95% CI: 0.28% to 2.2%) for the worst case scenario of a 50-year-old female smoker receiving 25 annual LDCT scans. This compares to a 17% risk of developing lung cancer (112). Berrington de Gonzalez estimated the cumulative risk of excess death from lung cancer from LDCT screening in 50-year-old smokers to be 2 per 10,000 men screened and 5 per 10,000 women screened. Additionally an estimated 3 cases of breast cancer per 10,000 women screened may occur (113). The NLST estimated the number needed to screen (NNS) to prevent one death from lung cancer was 320, equating to a rate of 30 fewer deaths per 10,000 screenees (13) a larger benefit than the radiation harm particularly as the cancers induced occur after a delay of many years and the lives saved are over the short term. Estimates from the ITALUNG RCT reached similar conclusions with an estimated 1.1 excess deaths per 10,000 screenees compared to approximately 15-100 lives saved per 10,000 screenees (women and men respectively) assuming a 20% mortality reduction from screening (114). Thus the radiation risk-benefit ratio of LDCT screening appears quite favourable in older populations of smokers.

Adverse events

Adverse events may result from investigation of LDCT findings. As 25-50% of screenees may have one or more nodules detected, a potentially large reservoir of patients at risk exists. In the NLST the cumulative chance of a positive screening scan was 39.1%.

Despite guidelines (115), significant variation in pulmonary nodule biopsy rates (14.7 to 36.2 per 100,000 adults) and complication rates have been found between hospitals in the USA (116). The risk of haemorrhage and pneumothorax requiring intercostal catheter drainage (ICC) were 1.0% and 6.6% respectively. Complications were associated with an increased length of stay and risk of respiratory failure. Those at highest risk were smokers, persons aged 60 to 69 years, and those with COPD, i.e., the types of patients targeted for screening. LDCT screening study adverse event rates may be slightly higher than the above study but this probably reflects more rigorous, prospective reporting. There appears to be no standard way of defining or reporting adverse event data which makes some studies difficult to compare directly. 'Number of events per 10,000 scans' may be a useful metric to allow cross-study comparison.

A study of 4,782 participants (117) screened using the I-ELCAP protocol reported a biopsy rate of 2.6% (n=127) including 110 percutaneous CT-guided fine-needle aspiration

biopsies (CT-FNA). 13% of CT-FNAs were complicated by a moderate-to-large pneumothorax requiring ICC or hospitalization. Overall 16% of biopsies were for benign disease (117). Using a volumetric-based protocol, NELSON reported the surgical diagnostic procedure rate as 1.2% in round one and 0.8% in round two; 32/92 (35%) and 13/61 (21%) procedures in each round were for benign disease. Very few CT-FNAs were performed: 5/13 CT-FNA in round one and 3/3 FNA in round 2 showed benign disease. Across both rounds bronchoscopy diagnosed cancer in 111/247 (45%) procedures-a lower than expected figure likely reflecting peripheral tumour location. Complication rates were not reported (50).

The PLuSS study (118) screened 3,642 participants using an in-house protocol. 82 (2.3%) underwent surgical procedures (thoracotomy or VATS), twenty-eight of whom (34%) had benign disease. The study investigators cited "an apparent community bias toward aggressive intervention" for indeterminate lung nodules.

At baseline, 27.3% in the NLST LDCT group had a positive scan result (13). 155/7,191 participants had a percutaneous diagnostic procedure (CT-FNA in 120) and 297 (4.1% of positive scans) had a diagnostic surgical procedure (thoracotomy, thoracoscopy, mediastinoscopy or mediastinotomy) including 197 thoracotomies. Across all three screening rounds (75, 126 screenings), 164/673 (24%) of surgical procedures in the LDCT group resulted in a non-cancer diagnosis. 191/673 (29%) of participants whose most invasive diagnostic procedure was surgical experienced at least one complication; in 80 (12%) this was classified as major. Only 14 of 99 (14%) participants who underwent a needle biopsy as their most invasive diagnostic procedure experienced one or more complication and none were major. 16 participants (10 with lung cancer) died within 60 days of an invasive diagnostic procedure, but it is not known whether death resulted directly from the diagnostic procedure. Put differently, 33 per 10,000 screenees suffered major complications during any diagnostic evaluation, but complications following bronchoscopy or needle biopsy were low, 1.5 and 0.7 per 10,000 screenees respectively; the frequency of death occurring within 2 months of a diagnostic evaluation was 8 per 10,000 (16). I-ELCAP has not reported its rates of diagnostic procedures or complications.

CT-FNA appears safe with a complication rate of 13-14% and good concordance of biopsy result with resected pathological specimens histology (119). Bronchoscopy on the other hand, although safe, may have a lower yield for small, peripheral cancers detected by screening, although newer techniques such as endobronchial ultrasound and electromagnetic navigation may be able to improve yield (120,121). Surgical procedures have major complication rates of 12% but around 20-35% of cases are ultimately diagnosed with benign disease. This has an impact on cost-effectiveness.

Although ultimately the decision to resect an indeterminate nodule is a clinical one, given the high proportion of reported benign disease detected by screening, a positive tissue diagnosis prior to surgical resection is desirable. As demonstrated by the NELSON study, definite growth over a three month interval was due to benign disease in up to one third of cases. To date most studies have been run from expert tertiary centres where CT-FNA is available as the initial diagnostic procedure for small peripheral lesions. It is likely that strict governance and quality assurance will be needed to keep unnecessary biopsies and resections to a minimum.

Lung-preserving surgery

As reviewed by Blasburg *et al.*, evolving surgical technique, the recognition of good prognosis for small tumours, especially with a high GGO component, and the on-going risk of subsequent tumours, has turned attention to 'lung preserving' surgery (anatomical segmentectomy and wedge resection) as an alternative to lobar resection for small tumours (122). Two randomized controlled trials which will hopefully be able to answer this important question are currently recruiting [CALGB 140503 and JCOG0802/WJOG4607L (123)].

Quality of Life (QoL)

Three studies have reported generic health-related QoL (HRQoL), anxiety and lung-cancer specific distress data from approximately 2,500 screening participants (124-126). All found some transient negative psychological effects for participants who received an indeterminate or suspicious screening result. These effects subsided fairly rapidly such that there were no significant differences in HRQoL between baseline and 12-24 months follow-up. The NELSON study reported that half the participants found waiting for their baseline CT scan results 'discomforting', but that an indeterminate result at the second round of screening had no impact on HRQoL. This suggests that minimizing the waiting time for test results is beneficial and that participants soon accept that an indeterminate scan result does not necessarily warrant high anxiety (124,127).

Smoking cessation

Smoking cessation is important not only for future risk reduction in participants without cancer, but may also improve the prognosis of those diagnosed with early stage lung cancer (128). Screening for lung cancer may be a "teachable moment" increasing motivation to quit, particularly if the participant receives an abnormal CT scan report (129-131). As successful smoking cessation programs may also make screening more cost-effective (99), and smoking cessation assistance 'adds value' to screening in several ways, it should be a core component of any lung cancer screening program.

Knowledge gaps

Despite the positive result from NLST, screening outside of a research trial should be conducted in a controlled environment with careful risk assessment prior to recommending screening and careful analysis of all outcomes to ensure quality. Two international workshops have considered the current state of evidence and future directions for research. Areas that need addressing were highlighted including: (I) how to optimise identification of high-risk individuals; (II) Screening protocols (e.g., screen interval, number of screening rounds); (III) Definition of a positive screen result; (IV) Management of indeterminate nodules; (V) Diagnostic and therapeutic interventions for suspicious nodules; (VI) Integrated smoking cessation programs; (VII) The role of early detection biomarkers in individual lung cancer risk assessment; (VIII) The rate of overdiagnosis. Important steps will be to standardise equipment and image quality, nodule analysis and interpretation, and participant follow-up and outcome reporting (93,132). Some of these areas are discussed below.

Overdiagnosis

Overdiagnosis is difficult to ascertain (see Box 2 for definition). It was estimated at 13% in the NLST-the relative difference between 1,060 cancers detected in LDCT arm and 941 cancers detected in control arm (13). However this figure has been criticised as an underestimate (133) on the basis that the appropriate denominator should be the number of lung cancers detected in the control group *during the screening period* (n=470), not at the end of follow-up (n=941), making overdiagnosis closer to 25%, a figure similar to that estimated by the Mayo LDCT study on the basis of VDT (37). However even this figure may be an underestimate if the CXR screening arm is also subject to overdiagnosis (133). Against this, subset analysis of the PLCO cohort who met NLST eligibility criteria (n=30,321) found similar numbers of lung cancer cases in the CXR and the non-screened arms (518 *vs.* 520 cancers respectively after 6 years' follow-up) (12). It is likely that only the European trials comparing screening to usual care (i.e., no screening) will be able to give a true estimate of overdiagnosis (90). This question therefore remains unanswered at present.

Screening interval and length of follow-up

The appropriate screening interval should provide a favourable ratio between disease control and screening costs (134). The MILD trial recently published their findings from a three-arm RCT of observation *vs.* annual *vs.* biennial screening in 4,099 participants (89). Stage distribution and resection rates were similar in the two LDCT arms. The cumulative 5-year lung cancer incidence was highest in the annual LDCT group compared to biennial and control groups (620/100,000 *vs.* 457 and 311 respectively, P=0.036). Adherence to the screening protocol was >95% in each LDCT arm but median duration of follow-up was only 4.4 years. Recruitment fell significantly short of the planned 10,000 participants meaning the study was underpowered to detect mortality differences. Also, differences in characteristics of screened and non-screened groups (such as smoking status, smoking intensity and lung function) raise doubts about the adequacy of randomization (135). Long-term follow-up results from this study may be more informative. The NELSON study, in which participants are screened at Year 1 (baseline), Year 2 and Year 4, i.e., a two-year gap between the second and third scan, could also inform on optimal screen interval when Year 4 results are reported. As previously mentioned, data gathered at baseline scan (i.e., presence of radiographic emphysema) may be useful in determining risk and thus optimal screening interval (68). Regarding duration of screening, the NLST LDCT arm detected 649 cancers after a positive screening test (270 at baseline and 168 and 211 at years 1 and 2 respectively) and 367 in participants who either missed the screening or were diagnosed after completing the trial screening phase (median follow-up 6.5 years). This suggests that cancer detection rates (i.e., cancer risk) do not drop significantly over time and that on-going screening may be required. Accordingly, current guidelines suggest annual screening until the age of 74 (14,16) or 79 (15).

Recruitment

Recruitment strategies have varied between studies, most commonly direct mailing and/or media releases, but some used general practitioner referral (84,88). Smokers, by definition are less risk averse than non-smokers, at least in terms of their health. The decision to enter a screening trial is a complex balance of factors including acceptability of screening methods, risk perception, altruism, and self-interest (136). Inevitably, volunteers in any trial are self-selected and contribute to the 'healthy volunteer' effect. This may result in overly optimistic outcomes (e.g., better screening compliance, higher smoking cessation rates) or overly pessimistic outcomes (e.g., lower effectiveness as lower-risk individuals benefit less from screening).

Both the NLST and NELSON studies found some differences between their study populations and eligible general population; Participants were younger and less likely to be current smokers and had higher education levels (a proxy for socio-economic status). These differences were considered minor, meaning that a significant healthy volunteer effect was unlikely (81,137).

Risk stratification

Risk stratification has been applied at a basic level with most

studies adopting the ELCAP strategy of screening older persons with a smoking history. Although age and tobacco smoke exposure account for the vast majority of lung cancer risk it is well recognised that other risk factors such as family history, socioeconomic status, occupational exposure and COPD contribute (138). Further risk stratification using other readily available information may be able to improve screening efficiency by excluding lower risk participants (139). Various models have been proposed, the largest derived from PLCO Trial data and recently updated (140,141). A retrospective analysis of this model applied to the PLCO dataset found that it was more efficient in comparison to the standard age- and smoking-based NLST entry criteria improving sensitivity from 71% to 83% (P<0.001), positive predictive value from 3.4% to 4.0% (P=0.01), and maintaining specificity (63% each). Use of the risk model to select screenees would have missed 41.3% fewer lung cancers (141). Prospective evaluation of another risk model is being undertaken by the UK Lung Cancer Screening Trial (142). Risk stratification may enhance screening effectiveness and cost-effectiveness by increasing lung cancer prevalence and incidence and reducing false-positive scan results. Although risk stratification makes intuitive sense it has not been proven experimentally, thus screening guideline recommendations diverge [recommend use of published risk model (15), informal risk assessment (14), no recommendation (16)].

Screening implementation

Generalization of findings from tightly controlled trial situations to large-scale mass screening programs require uniform standards and high quality control in order to be able to accurately track and assess nodules over time (132). Lung cancer screening is more than simple provision of a CT service; It is as a long-term commitment requiring extensive infrastructure to allow for invitation and recruitment; quality improvement; workforce/facility capacity for screening, diagnosis and treatment; health professional training; participant information and support. On-going evaluation and monitoring of the program is essential to ensure high standards of care are met and delivered in a consistent and acceptable way (134,143).

Future research

Minimally invasive, inexpensive tests to identify individuals at highest risk of lung cancer most likely to benefit from screening or to distinguish benign from malignant screen-detected nodules would represent major advances in lung cancer screening. Promising new technologies in this regard include analysis of blood for circulating microRNAs and exhaled breath for volatile organic compounds (144-146). Most recent LDCT screening studies included biomarker collection in their protocols, so we can expect exciting new insights into these areas in the near future.

Conclusions

The results of the landmark NLST have proven the long-held belief that screening for lung cancer can save lives. Understandably, as a new intervention, many questions remain making generalizability to non-US settings difficult. Over the next few years, further analysis of NLST data and maturation of other important trials will be able to fill these knowledge gaps allowing the lung cancer community to evolve and refine the way we screen.

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