Lung Cancer Screening with Low-Dose CT in Europe

Subjects: Oncology

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Lung cancer screening (LCS) with low-dose computed tomography (LDCT) was demonstrated in the National Lung Screening Trial (NLST) to reduce mortality from the disease. European mortality data has become available from the Nelson randomised controlled trial, which confirmed lung cancer mortality reductions by 26% in men and 39–61% in women.

screening lung cancer mortality reduction low dose computed tomography

1. Introduction

Lung cancer is responsible for ~270,000 deaths annually in Europe, more than for any other cancer [1]. Despite long-standing interest in the European medical community for lung cancer screening (LCS) with low-dose computed tomography (LDCT) for reducing lung cancer mortality, supportive European data has only recently become available from a European Randomised Controlled Trial (NELSON). Use of LDCT-LCS in NELSON was associated with lung cancer mortality reductions of 26% in men and 39–61% in women [2]. These results have convinced experts and many politicians to advocate for LDCT-LCS implementation in Europe. However, the economic impact of LDCT-LCS still needs to be assessed, and guidelines for an effective and safe screening need to be formulated.

2. Eligibly Criteria for LDCT-LCS

2.1. Selection of High-Risk Individuals for LDCT-LCS

Screening is more effective in high risk individuals for lung cancer, but the selection of the population at risk amenable of screening (the common denominator to all evaluations) is of the utmost importance [3][4]. Current recommendations for high-risk individuals are based on either (a) criteria (mainly age and smoking history) originally used by the National Lung Screening Trial (NLST) [5], or derivative criteria, such as those introduced by the United States Preventive Services Task Force (USPSTF) [6][7] and the Centre for Medicare and Medicaid Services [8]; or (b) risk thresholds estimated by validated lung-cancer risk-prediction models.

Identifying a lung-cancer risk model will help select high-risk individuals for LDCT-LCS in Europe is essential for the future of secondary prevention tools. Two candidate models—$PLCO_{M2012}$ and LLP_{v2}—may be suitable in this task. The former has been externally validated in North American datasets. The risk threshold should be either >1.5, >2 or more, over 6 years for

$PLCO_{M2012}$ and 2.5% or more over 5 years for LLP_{V2}, depending on the national budget available. This recommendation is likely to change in the near future as prediction tools will become more extensively validated in Europe.

2.2. Inclusion of Asbestos-Exposed Individuals in LDCT-LCS

Asbestos is a major occupational and environmental carcinogen causing several cancers, particularly mesothelioma and lung cancer [9]. It was estimated in 2014 that 5–7% of newly diagnosed lung cancers were due to asbestos exposure [10]. The long latency of asbestos-related cancer development and the increasing life expectancy, surveillance and screening of asbestos-exposed persons may be instrumental to increase the proportion of individuals being diagnosed with early stage disease [9][10][11]. The 2015 Helsinki Consensus Report [12] had in fact recommended LDCT-LCS in the following workers: (a) those with any asbestos exposure and a smoking history according to NLST criteria (smokers and former smokers, aged 55–74, with pack-year ≥30); or (b) those with asbestos exposure regardless of smoking history but who have an estimated risk equal to that of NLST [5] study population. However, there is only limited evidence to support the use of LDCT-LCS in asbestos-exposed persons and other exposed workers [13][14]. Furthermore, most studies investigating LDCT-LCS in asbestos-exposed persons did not perform risk estimation to identify high-risk individuals for asbestos exposure [10]. Some lung-cancer risk-prediction models included asbestos exposure as a risk factor [15], but no validated model has comprised a detailed evaluation of asbestos variables in never-smokers. Such models are necessary to make LDCT-LCS in asbestos-exposed persons cost-effective and useful [10][12][16]. In the meantime, the criteria proposed by the 2015 Helsinki Consensus Report [12] for LDCT-LCS in asbestos-exposed persons may be adopted.

Unfortunately, identifying individuals exposed to asbestos is often a challenging task. In theory, asbestos-exposed persons might be monitored through databases generated by asbestos-using workplaces as per EU Directive 2009/148/EC. However, such data are often difficult to get. Use of validated questionnaires and checklists administered by trained interviewers are the most reliable means to identify persons with a work significant history of asbestos exposure [12][13][14][16][17], particularly when corroborated with data coming from the literature or databases on asbestos fibres content per air volume unit in workplaces [18][19]. Nevertheless, as people change jobs, it can be challenging to reconstruct occupational history and make precise estimations of asbestos exposure. Therefore, it is advisable cross-checking information upon questionnaires against data originated by trade unions, workers' compensation and employment records, individual charts with diagnosed pleural plaques at chest X-ray and social security databases [17].

2.3. The LCS Recruitment Challenge in Europe

One of the major unresolved challenges to ensure optimal implementation of LDCT-LCS is participation, which is likely to result in lower accrual than other screening programs [20][21]. In particular, the participation rate of more-deprived socioeconomic status (SES) individual groups was low enough to be of concern for the successful implementation of LCS programs [20][21]. This is due to the over-representation of high-risk individuals in the more-deprived SES groups, despite that over 40% of detected lung cancers were in the most-deprived quintile people. This strong association with lower SES indicates that more-deprived groups will have to be included in future screening programs to reduce the existing inequalities in lung-cancer mortality. Although it might be difficult to recruit (former) smokers for intervention arms, benefits for the compliers may be substantial and even more than expected, since they might also benefit from other early evidence-based interventions, given the additional risk for other diseases.

This represents the most challenging balance to achieve between less costly and unsystematic approaches on the one hand (via open clinics, vans, advertisements), which likely will accrual lower risk individuals and systematic approaches on the

other hand (via health registers, GP registers, questionnaires, and online surveys), which ensure better filtering of high-risk people but may be yet scarcely available and/or of unpredictable quality. Therefore, inviting individuals to LCS programs via existing and tested systems of patient accrual may be preferable. For example, in the Netherlands, which has population registries, the cancer-screening organisations could send a standard letter with just three questions on lung cancer concerns, residence characteristics (e.g., pollution) and smoking habit, along with a link to an online calculator [22]. However, even in the NELSON study, there was evidence that participants had slightly better self-reported health, with younger, more physically active, higher educated and more often former smokers comparable with eligible non-responders potentially more representative of the whole audience of lung cancer in the general population [22].

All these general approaches do not consider how different individuals will respond to different methods of invitation. Recruitment with a more “tailored approach” may be a solution, in which tailoring is used to (1) ensure all groups respond optimally; (2) allow risk assessment to be completed; (3) ensure that invitations optimise participation. This approach is especially important where population registries do not exist or are incomplete. The UK Lung Screen Uptake Trial (LSUT), which used a direct invitation strategy by primary care doctors in a deprived population, had a 53% participation rate [23]. The authors created a supportive and nonjudgmental service, acknowledging that the invited generation had been previously not as informed of the risks of smoking and, thus, avoided mentioning smoking, smoking cessation and risk where possible at the invitation stage. As a matter of fact, a potential risk of LCS, in the absence of adequate information and educational policy on smoking quitting, would be to create the false idea of an a priori protective effect of screening in subjects who continue to smoke undaunted.

2.4. Biomarkers for the Selection of Individuals for LDCT-LCS

Biomarkers may improve the effectiveness of screening by (a) refining the selection of persons for screening; (b) providing data indicating whether or not indeterminate screening-detected nodules are malignant; (c) predicting response to therapy and outcome. In theory, a single biomarker could be useful in all settings, but it is expected that risk-related markers will be more useful for accruing individuals to screening, whereas disease-related markers (e.g., tumour DNA) will be more useful in nodule management and predict outcome [24]. A risk marker for screening selection needs to be cheap, as it will be used on large numbers of people, whereas a disease marker has less stringent cost requirements, as it will be used on far fewer people. Irrespective of intended use, any biomarker should be able to detect lung cancer early in its preclinical phase, needs to be reliable, should be minimally invasive (e.g., applicable to biological fluids), be cost-effective and commercially available to disseminate its application.

Pre-diagnostic serum microRNA signatures have also been reported associated with lung cancer. Samples from 939 participants (69 with lung cancer; 870 disease-free) in the biological randomised Multicentre Italian Lung Detection Trial (BIO-MILD) were analysed using a quantitative PCR-based assay to derive a plasma microRNA signature cluster (MSC) [23]. The MSC had 87% sensitivity and 81% specificity across both arms and was able to predict the occurrence of lung cancer up to two years before its detection on CT scan [23]. Similarly, when validated in participants of the Continuous Observation of Smoking Subjects (COSMOS) study, the signature decreased to 77.8% sensitivity and 74.8% specificity [25][26].

Various other non-blood biomarkers have also been assessed for association with lung cancer, including volatile organic compounds from exhaled breath [27][28], condensate from exhaled breath [29], and bronchial epithelial cells in sputum after removal of non-bronchial cells [30]. Results are yet preliminary and need further investigation.

To conclude, biomarker assessment may improve eligibility selection for LDCT-LCS and management of screening-detected nodules. Panels of markers appear more promising than individual markers. However, most studies have assessed relatively small numbers of cases and several used samples from patients with a confirmed lung-cancer diagnosis. Larger studies on pre-diagnostic samples from longitudinally followed populations or screening cohorts are thus necessary to fully validate the performance of biomarker panels and justify their routine use in screening. Multinational studies on lung cancer-associated biomarkers are ongoing on mixed (smokers and non-smokers) and at-risk cohorts recruited to prospective screening trials. These studies are expected to provide more robust evidence on biomarker utility, but cost-effectiveness analysis will need to be nonetheless carried out for any new potential biomarker.

2.5. CT Protocols and Diagnostic Algorithms for Management of Nodules at Baseline and Repeat LDCT Scans

LCS is challenging at baseline, as findings have accumulated over a lifetime and may be of no clinical concern (length time bias). To minimise unnecessary harm and cost of work-up prior to the first annual repeat screening, work-up should be limited to participants with the highest suspicion of lung cancer while still aiming to identify small, early lung cancers. Cancers found in repeat rounds of screening are typically more aggressive and, thus, require work-up, so the timing should be different [31][32][33][34].

To assess published diagnostic protocols, a PROSPERO-registered systematic review of reports in English published before 9 November 2018, is currently underway. The primary outcome is the efficiency of the protocol (proportion of positive findings vs. lung cancer) by nodule type at baseline and repeat scans; secondary outcomes are the number of lung cancers detected per invasive work-ups, benign resection rate, and false-positive rate. Of the 9629 potential articles identified, only nine articles on eight separate studies qualified for inclusion: these included an international multi-institute study on 25,506 participants [35], a single institution study in Korea on 6406 participants [36], a single institution study in Ireland on 449 participants [37], a single institution study in Italy on 5201 participants [38], a 12-institute study in New York State on 6295 participants [39], a single institution study in Israel on 842 participants [40], a single institution study in Germany on 187 participants [41], and a single institution study in Taiwan on 3339 participants [42]. Three studies [35][39][40] used the I-ELCAP nodule-management protocol, whereas the others used separate study-specific management protocols. Preliminary results indicate that reporting on outcomes by nodule type and rounds of screening is limited, making it challenging to compare the efficiency of the different protocols.

In Europe, the four main protocols that have been used are the European consortium protocol based on the NELSON trial [2]; the I-ELCAP protocol [43], which has been used in Italy, Spain, and Switzerland; the American College of Radiology's LungRADS; the British Thoracic Society Guideline (BTS) [44], which does not distinguish between incidental and screen-detected nodules [45]. A comparison of the baseline round of screenings of three of these protocols has been performed [35]. It determined the efficiency ratio (ER) of each recommendation by dividing the number of participants recommended for that work-up by the number of resulting lung-cancer diagnoses, a lower ER indicating that fewer participants undergo additional procedures for each diagnosis of lung cancer. For I-ELCAP, LungRADS Scenario 1 and Scenario 2, and the European consortium, ERs were, respectively, the following: for immediate work-up, 2.9, 8.6, 3.9, and 5.6; for delayed work-up, 36.1, 160.3, 57.8, and 111.9; overall, 13.9, 18.3, 18.3, and 31.9; for biopsies, 2.2, 8.1, 3.2, and 4.4. A low ER for biopsies is particularly important, as biopsies are invasive procedures, and unnecessary biopsies (i.e., of non-malignant nodules) should be minimised. All protocols use an initial LDCT in the screening round to determine who requires further short-term screening before the next annual repeat. The threshold values and the timing of the short-term follow-up are different. The important

point of the comparison is that small differences in threshold values can lead to many unnecessary diagnostic work-ups and biopsies, as shown by the outcomes.

The BTS guideline [44] is the first to mandate the use of semi-automated volumetry in nodule management, and it is the recommended nodule-management method of the English Lung Health Check program.

All protocols should be reviewed and updated to incorporate advancing technology and knowledge, including the definition of positive results and the timing of further work-up. The work-up recommendations should be developed together with the relevant medical specialities, and it must be recognised that the LDCT findings are in asymptomatic participants and not in people seeking clinical care as prompted by symptoms.

For the future, machine learning may help in the detection and characterisation of nodules. Several publications have demonstrated the use of ML to characterise nodules from an image. Ardila et al. achieved 94.4% AUC performance on a large number of cases of the National Lung Cancer Screening Trial, and validation sets [46]. This creates an opportunity to optimise the screening process through IT assistance and case automation by enhancing advanced learning models in order to increase consistency and adoption of lung cancer screening worldwide.

2.6. Considerations on Volumetry and Doses

The NLST deemed ≥4-mm-sized nodules discovered at baseline screening to be suspicious for malignancy: this low threshold resulted in a high recall rate (27%) and a low positive predictive value (3.8%) [5]. A retrospective analysis of data from NLST and I-ELCAP suggested that the nodule-positivity threshold could be increased to 6 mm or even 8 mm (~300 mm^3) to correct for the high false-positive rate in NLST [5].

The NELSON study assessed nodule volume and estimated volume-doubling times as an indicator of nodule growth rate and included a third category of undetermined nodules. Compared with NLST, this approach reduced positive test results at baseline to 2.6% of screened subjects and increased positive-predictive value to a satisfactory 36% [47].

Regarding the calculation of nodule volume, direct conversion of mean or maximum axial diameter to volume assuming sphericity leads to an overestimation of nodule volume as compared with semi-automated volumetry [48].

For any given volume, new nodules found at follow-up CT have a higher probability of being lung cancer than those detected at baseline [49][50]. Therefore, new (incident) nodules with volumes of 30–200 mm^3 should be classified as indeterminate and require a repeat scan at 3 months to calculate the volume-doubling time; new nodules ≥200 mm^3 should be referred to clinical work-up; in some occasions, a short observation period of one month and antibiotics can help reduce false positives for inflammatory disease at surgery or invasive procedures [38].

One of the concerns of CT screening is related to radiation exposure. There is no consensus on what level of radiation is considered ‘low-dose’. However, a low-dose lung cancer screening CT scan should be performed based on technical specifications ensuring that the quality of the screening and the radiation dose is in compliance with ACR-STR recommendations [51][52].

The assessment of cancer risk from radiation is based on the linear no-threshold model [53] and on data collected from occupational studies and from atomic bomb survivors. The risks are thus based on models generated from studies on people

exposed to high levels of radiation; therefore, the linear no-threshold model stands as a precautionary recommendation that follows a conservative approach.

2.7. Work-Up and Treatment of Screening-Detected Nodules

To ensure successful LCS, it is essential to reduce to the minimum the number of invasive procedures for benign disease [54] and to avoid overtreatment of very early cancers or precancerous lesions. The best way to reduce surgery for benign lesions is to have an accurate preoperative/diagnostic algorithm, as this reduces the number of indeterminate nodules referred for surgery. In pre-specified cases, time should be allowed for watchful waiting to verify growth and calculation of volume-doubling time of the nodules and for repeated biopsies to substantiate malignancy. According to the National Comprehensive Cancer Network guidelines [55], a preoperative biopsy can be avoided when a strong clinical suspicion of Stage I or II lung cancer is present if the lesion is peripheral and if diagnosis can be easily obtained intraoperatively before resection [54].

The recommended threshold of surgical resection for benign disease should be below 10%. A percutaneous biopsy can assist in minimising benign resection rate and frozen section times [56]. Brock score can be used to triage patients between surveillance and further investigation [57].

For small and ground-glass nodules associated with early-stage cancers, sublobar resections—once reserved for functionally compromised patients—are being reconsidered. Limited resection, especially anatomical segmentectomy, may carry similar oncological outcomes as standard lobectomy, as demonstrated in retrospective studies [58][59][60], but the non-inferiority in oncological outcomes is still being assessed (trials JCOG 0802 and CALGB 140503) [61][62].

Minimally invasive techniques should be encouraged, post-operative 30-day mortality should be maintained lower than 1%, and major morbidity kept lower than 5%; the surgeons should be skilled in performing complex, minimally invasive anatomical sublobar resections (VATS or robotic segmentectomies) [63].

Recently published recommendations on the use of stereotactic body radiotherapy (SBRT) vs. surgery in early-stage non-small-cell lung cancer indicate a few main points when selecting patients for local radical treatment, [64] including: (a) for fit-for-surgery patients, SBRT is not contemplated outside the context of clinical trials, with the choice discussed within the MDT; (b) for high-risk patients, SBRT can be considered after adequate discussion within the MDT, provided patients are informed of decreased treatment-related risks and the unknown long-term outcomes; (c) SBRT should be carefully selected for central tumours, due to the increased risk of severe toxicity, one possible recommendation would be that the high-risk setting be defined by an FEV1 or a DLCO < 50%, or when there is a combination of risk factors, such as advanced age, impaired pulmonary function, pulmonary hypertension, or poor left-ventricle function. Nevertheless, the patient should have the final word after discussion with an expert thoracic surgeon. To aid the selection of candidates with borderline cardiopulmonary function, international guidelines and institutional adaptations of risk models are available [65][66]. If the MDT consensus and patient's preference favours surgery, high-risk candidates should undergo sublobar or wedge resections through a minimally invasive approach [47][64][67]. For patients with second primary and multiple tumours, it is strongly recommended to discuss the patients within the MDT, and EBUS or mediastinoscopy be performed to rule out mediastinal involvement [68]. SBRT and/or surgery can be part of the same protocol for local aggressive treatment of oligometastatic disease [69].

2.8. Smoking Cessation and Other Initiatives within LDCT-LCS

Interventions to Stop Smoking

Patients undergoing LDCT-LCS may be particularly likely to consider stopping smoking, so may benefit from a smoking cessation (SC) initiative. However, data on the effectiveness of SC interventions in the context of screening are limited [70][71][72].

Five studies on smokers undergoing LCS without any formal SC program reported that 22% had stopped smoking two months after screening [73][74][75][76][77][78], 8% had stopped after six months [79], and ~14% were found, by biochemical assay, to be non-smokers a year after screening [80][81]. Ten studies reported outcomes of help given to all smokers undergoing screening [82][83][84][85][86][87][88][89][90][91]. Three studies investigated the effect of giving printed material only to encourage SC at randomisation. There were no significant differences in quit rates between the screened and control arms at two years [82][83], although in two studies screened-arm participants who underwent additional investigations were more likely to quit than controls or screened persons with a negative result [82][83]. One study reported that participation in LCS increased SC rates above that of the general population [84].

A small number of studies have compared SC interventions in LCS settings. No differences were found for standard written self-help materials vs. a list of internet SC resources [92], tailored vs. standard written SC information [93], or a brief SC counselling session on the day of screening vs. self-help printed materials and quit-line details [94]. One study testing the efficacy of six telephone-based services delivered by trained counsellors vs. self-help SC resources reported significantly higher biochemically verified 7-day point prevalent quit rates at 3-month follow-up vs. control (17.4% vs. 4.3%) [76].

Due to the small number of studies testing SC interventions at LCS have large variations in setting, participants, intervention, and outcome measure, they do not allow direct comparisons to be made. Thus, it is difficult to draw conclusions on the optimal intervention to administer. The SCALE collaboration in the US was established to support projects testing SC interventions delivered in LCS settings involving LDCT, and to build an evidence base for effective approaches [95].

Although data are lacking, the evidence does suggest that LCS in itself is a motivator for SC. However, more intensive SC interventions are needed to optimise quit rates within LCS programs, with smokers who do not receive the ‘all clear’ probably being more receptive.

2.9. Incidental Findings

Incidental findings are findings unrelated to lung cancer detection that are found because LDCT is a sensitive test for many different conditions. Correct management of incidental findings has the potential to increase benefit and cost effectiveness. However, incorrect management may lead to over-investigation and to treatment that may increase costs and harm patients.

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