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THE ROLE OF IMAGING IN SCREENING SPECIAL FEATURE: REVIEW ARTICLE

Lung cancer screening—low dose CT for lung cancer screening: recent trial results and next steps

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ABSTRACT

Screening for lung cancer using low-dose CT has already been implemented in North America following the results of the National Lung Screening Trial. Outside North America, clinicians and researchers are addressing issues that may have a major impact on the success of screening programmes by reviewing results of existing trials and by designing new research and pilot programmes. This review summarizes the work that has been done to try to answer the remaining questions and highlights potential barriers which may affect screening uptake and cost-effectiveness.

INTRODUCTION

The National Lung Screening Trial (NLST), completed in 2010 in the USA, showed a reduction in lung cancer specific mortality rate of 20% and in addition an all-cause mortality rate reduction of 6.7% comparing screening by low-dose CT (LDCT) with chest X-ray.¹ The largest European randomized controlled trial, the Dutch-Belgium NELSON trial, is expected to report on mortality in 2017–2018 and this may be followed by pooling of data from the European trials. Annual screening for lung cancer with LDCT has been recommended by the United States Preventive Services Task Force in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years.² It has also been recommended by the Canadian Taskforce on Preventive Health Care for people aged 55 to 74, with the same smoking history, but only annually for 3 consecutive screens.³ Outside North America, clinicians and researchers are addressing issues that may have a major impact on the success of screening programmes by reviewing results of existing trials and by designing new research and pilot programmes. Previously, the results of the primary outcome of the NELSON trial (lung cancer mortality) were awaited, but many consider current evidence for mortality reduction sufficient to plan implementation. In the UK, the National Institute for Health Research Health Technology Assessment process is awaiting a commissioned report on the clinical and cost-effectiveness of CT screening, due to publish findings in July 2017. In the meantime, pilot screening initiatives have begun in several

cities, in the main fuelled by the ongoing high mortality rate and belief that LDCT screening is effective. In this article, we review the progress made with key issues that will be important in ensuring that CT screening programmes benefit the most people in a cost-effective way.

Remaining questions and barriers to screening uptake

Selection for screening

In order to ensure that a screening programme is cost-effective and potential harms are minimized optimal selection methods need to be explored. NLST used age and cumulative smoking exposure (pack-year history), however one criticism of this approach has been that it does not take other important factors such as family history or smoking intensity into account and may therefore include some people at lower risk and exclude some at higher risk. It was estimated that 26.7% of patients with lung cancer and 8.6 million of the general population in the USA would have met the screening eligibility criteria used in NLST.⁴ The United Kingdom Lung Screening Trial (UKLS) used the Liverpool Lung Prediction (LLP_{v2}) model to select those at high risk of lung cancer (5-year lung cancer risk >5%) and had a higher lung cancer detection rate at baseline (2.1%) compared with NLST or the NELSON trial.^{1,5} A study used the prostate lung colorectal and ovarian (PLCO)_{m2012} model in place of the NLST selection criteria and this suggested that 8.8% fewer people would have been screened and 12.4% more cancers would have been detected.⁶ To date,

Table 1. Lung cancer incidence risk prediction models

Model	Development dataset	Outcome	Number of subjects	Age range (years)	Smoking status	Variables included in model
Bach model ⁷	Carotene and Retinol Efficacy Trial	Lung cancer incidence (1-year iterative)	1,8172	50–75	Current Ex	Age Asbestos exposure Smoking (duration, intensity, years since stopped) Sex
LLP model ⁸	LLP case-control study	Lung cancer incidence (5 years)	1736	20–80	Never Ex Current	Age Asbestos Pneumonia Family history Prior cancer Sex Smoking (duration)
PLCO _{m2012} model ⁹	PLCO Cancer Screening Trial	Lung cancer incidence (6 years)	8,3375	55–74	Current Ex	Age Race BMI COPD Family history Education Personal history of cancer Smoking (status, intensity, years since stopped)
Two-stage clonal expansion lung cancer incidence model ¹⁰	Nurse's health study, health professionals follow-up study	Lung cancer incidence (1 year iterative)	15,0543	30–75	Never Ex Current	Age Sex Smoking (status, duration, intensity, years since stopped)
Spitz ¹¹	University of Texas MD Anderson Cancer Center dataset	Lung cancer incidence (1 year)	3852	20–80	Current Ex	Age Dust Emphysema Family history Sex Smoking
Hoggart ¹²	European Prospective Investigation into Cancer and Nutrition dataset	Lung cancer incidence (1 year)	16,9035	35–65	Current Ex	Age Smoking

LLP, liverpool lung project; PLCO, prostate lung colorectal and ovarian.

around 20 risk prediction models to assess lung cancer incidence have been developed some of which may be employed to allow a more individualized risk stratification to select for screening.^{7–12} These are summarized in Table 1.

Other models have been developed which predict 1-year lung cancer mortality but this outcome is less useful in terms of selection for screening as it is likely to pick up more advanced disease. Many of these models are also derived from historical cohorts (e.g. the Knoke model used data from the American Cancer Society's first Cancer Prevention Study (CPS-1) which comprised patients diagnosed between 1959 and 1972) so are less likely to be applicable to a modern population.^{13,14}

The information required for the current risk prediction models could be easily obtained from primary care records or during a consultation, with possibly the integration of a web-based tool to allow screening selection. Work has shown that selection for screening using an individual risk assessment is superior to age and cumulative smoking exposure alone with a higher

sensitivity and specificity. However, the discriminatory power of the currently available models varied widely in validation studies, with PLCO_{m2012} performing the best with area under the receiver operating curve values of 0.77.¹⁵ It is suggested that an AUC value of >0.75 is needed to be adequate for the identification of high-risk individuals.¹⁶ Further work is needed in order to determine the optimal screening selection model for use in the UK population and to assess the cost-effectiveness of this, alongside an assessment of model performance at a variety of risk thresholds.

Screening interval

When looking at cost-effectiveness and harm minimization, determining the optimal screening interval is also important. Two of the European trials looked at screening interval as part of their design. The Multicentric Italian Lung Detection trial randomized patients to the control arm or to annual or biennial screening using LDCT. There was no difference in either detection rate or interval cancer rate between the two arms but the numbers of patients in each arm were small (1152 and 1151)

with low numbers of lung cancers detected (29 in the annual vs 21 in the biennial arm).^{17–19} The NELSON trial also looked at screening interval, with screening taking place at baseline and 1, 3 and 5.5 years from baseline (screening intervals of 1, 2 and 2.5 years). There were more late-stage screen-detected lung cancers in the 2.5-year interval compared with the 1-year interval (17.3% Stage 3B or 4 vs 6.8%). In addition there were more interval cancers (5 in year 1, 19 for the 2-year interval and 28 with a 2.5-year interval).²⁰ Sixteen (57%) interval cancers developed in the final 6 months of the 2.5-year interval, suggesting that 2.5 years between screens is definitely too long.

Modelling for the United States Preventive Services Task Force tried to address the balance of cost-effectiveness, false positives and mortality reduction looking at a variety of inclusion criteria based on age, cumulative smoking exposure and a screening interval of 1, 2 or 3 years. This suggested that annual screening between the ages of 55 and 80 for ever-smokers with at least 30 pack-years and ex-smokers who quit less than 15 years ago was the most advantageous strategy, which has been implemented currently in the USA.²¹ Furthermore a microsimulation modelling approach looking at a variety of age cut-offs, smoking exposure and screening intervals was performed on NLST data and population data from Ontario, Canada. This suggested again that annual screening was more cost-effective than biennial and that stringent smoking eligibility criteria should be adopted for maximal cost-effectiveness.²²

Risk stratification following baseline CT

The work described above did not take into account findings from both NLST and NELSON about the implication of a negative baseline CT on subsequent diagnosis of lung cancer. It is likely that this will be used to guide CT screening intervals. This individual risk stratification approach has been adopted (in reverse) by the breast cancer screening programme in the UK: annual screening rather than 3-yearly screening is offered to those with a genetic mutation or strong family history which may predispose to cancer. A retrospective analysis of the NLST data suggested that those with a negative baseline screen (a positive screen was defined as any non-calcified nodule ≥ 4 mm diameter, mediastinal mass, pleural disease or atelectasis in one or more lobes) had a lower lung cancer incidence (0.34 vs 1.02%) and lower mortality compared with the other screening participants.²³ The authors suggested that in this group annual

screening may not be necessary which could minimize harms from false-positive results and improve cost-effectiveness. The NELSON group also looked at those in whom the baseline screen was negative (defined as no nodule, nodules <15 mm³ or a previously detected nodule with a growth (change in volume) between scans of $<25\%$ or $\geq 25\%$ but a volume doubling time of >600 days). Their work showed that the risk of screen-detected lung cancer at 5.5 years strongly depended on the result of the first scan. Those with a negative baseline scan had 0.6% incidence of lung cancer at the final screening round compared with 1.6% in those who had indeterminate or positive scans at baseline.^{24,25} Further work still needs to be done to address in more detail which screening intervals (2 years or greater) may be appropriate in light of a normal baseline CT scan and whether this could be used alone or in combination with additional risk stratification.

Nodule management protocols

NLST did not employ a nodule management protocol other than defining a nodule of ≥ 4 mm in diameter as a positive test. No further protocol was applied to management of nodules. The NELSON trial specified different categories of nodule according to volume or diameter (if volumetry was not possible). However no protocol was specified once referral for a positive test was made to the clinical teams.²⁶ In contrast UKLS used a similar approach to NELSON but stipulated adherence to National Institute for Health and Clinical Excellence guidelines. Both NELSON and UKLS succeeded in reducing the number of false-positive tests but UKLS achieved both a lower benign resection rate and low additional investigation rate (Table 2).

The NELSON approach to nodule management used size and growth (volume doubling time) to try to reduce the number of false-positive screening test results. Those with nodule volumes of <100 mm³ or 5 mm diameter had comparable lung cancer likelihood as those with no nodules and those with a volume doubling time of >600 days likewise had very low lung cancer probability. These results formed the basis of the British Thoracic Society Guideline on the Management of Pulmonary Nodules, which provides a detailed, evidence-based algorithm for the assessment and management of pulmonary nodules.³² Importantly, this guideline shows how to manage nodules with a higher probability of malignancy to ensure invasive investigations and treatment are

Table 2. False-positive rates, resections for benign disease and complications in the main lung cancer screening trials

Trial	False positives % (95% CI)	Proportion undergoing invasive surgical procedure/resection for benign disease	Major complication associated with surgical procedure %
National Lung Screening Trial ¹	23.1 ^a (21.9–24.3)	24% (164/673)	12
DANTE ²⁷	22.9 (20.6–24.9)	22% (17/77)	29
Danish Lung Cancer Screening Trial ^{28,29}	7.9 (6.8–9.1)	16.6% (3/18)	38
Multicentric Italian Lung Detection ¹⁹	0.8 (0.6–1.1)	6.4% (5/78)	Not reported
NELSON ³⁰	1.2 (1.1–1.3)	23%	10.7
United Kingdom Lung Screening Trial ³¹	3.6 (2.9–3.5)	10.3% (4/39)	Not reported

^aIncluding clinically significant abnormalities, not suspicious for lung cancer.

minimized for benign lesions or lesions that are relatively indolent and may represent those that contribute to overdiagnosis.

New nodules on incident screens

The NELSON study also looked at the appearance of new solid nodules after baseline screening and the probability of these being malignant. Between 5 and 7% of individuals developed new nodules at each screening round and these new nodules were found to be lung cancer in 6% of participants. Nodule volume had a high discriminatory power in determining probability of malignancy, with a nodule size cut-off of $\geq 27 \text{ mm}^3$ having 95% sensitivity for lung cancer. As there seems to be a much higher likelihood of malignancy in these new solid nodules, even at a small size, more aggressive investigation and follow-up may be needed for interval nodules.³³

Radiologist numbers

There are concerns that thoracic radiologist numbers in Europe are currently insufficient to be able to successfully implement a lung cancer screening programme and numbers may need to increase substantially. Expertise in CT interpretation and characterization of pulmonary nodules is required to reduce the number of false-positive detections. The UKLS sought to evaluate the performance of appropriately trained reporting radiographers as an alternative to radiologists in detection and interpretation of lung nodules on CT. Although some radiographers compared favourably with radiologists, in general the radiographers had much lower sensitivity and higher numbers of false-positive detections per case.³⁴ It has been suggested that the radiographers may have a role as an assistant reader (either first or concurrent reader) and detected nodules could be presented to a radiologist for verification. This approach would need more detailed evaluation and assessment before implementation.

Smoking cessation

There has also been some concern that screening would offer false reassurance in those who smoke, leading to continued smoking, new or renewed uptake of the habit. The NELSON study showed smoking cessation rates of 14.5% in the screened arm and 19.1% in the control arm. These are substantially higher than the background rate of 6–7%.³⁵ A study of a subgroup of NLST participants showed that a false-positive screening result was associated with increased smoking cessation and negative screens did not seem to be associated with increased relapse.³⁶ Analysis of smoking behaviours in UKLS showed 2-year smoking cessation rates of 24% in the intervention group and 21% in the control arm (net trial quit rate of 22%) compared with a UK population cessation rate of 4%. Those who had a negative screening result were still more likely than controls to quit smoking (odds ratio [OR] 1.78; 95% confidence interval 95% CI [1.04 to 3.05]). In addition those who needed additional clinical investigation after their initial CT scan result had much higher odds of stopping smoking (OR = 2.42; 95% CI [1.53 to 3.82]).³⁷

Modelling shows that integration of smoking cessation interventions (varenicline and behavioural techniques) into a screening service improves the cost-effectiveness; however qualitative work performed in the UK in socially deprived communities has suggested that mentioning smoking cessation would be viewed as off-putting.^{38,39} Other qualitative work has shown that the idea of smoking stigma is seen as reason not to participate in screening so it is clear that further behavioural work needs to be done to evaluate optimal strategies to integrate smoking cessation into any lung cancer screening programme.⁴⁰

Screening uptake in the high risk population

An important consideration is uptake rates into a screening programme, as low uptake would render it non-viable.⁴¹ Recruitment into UKLS showed that those who were deemed (using risk stratification tools) to be at highest risk of developing lung cancer were least likely to take up the offer of screening.⁴² There are data to suggest that smokers view screening in a nihilistic way and perceive early detection to be of limited use and, as such, are less likely to consider screening participation.⁴³ Recruitment to and participation in lung cancer screening trials to date has tended to comprise more former smokers from more well educated backgrounds.^{42,44,45}

An analysis of those who declined participation in the UKLS trial identified several practical and emotional barriers. Key practical barriers cited were travel distance, lack of available public transport and costs of the journey or hospital parking. The most commonly cited emotional barriers were fear and avoidance of lung cancer information.⁴⁶ Work is ongoing to try to understand how best to maximize uptake when, and if, screening is implemented in the UK. One randomized controlled trial in London is currently testing targeted invitation material to see if uptake may be improved in this way, alongside some community-based screening pilots to try to overcome some of the practical barriers.^{47,48}

CONCLUSION

Since the publication of NLST, there has been extensive debate about the issues discussed in this article, with ongoing work underway to try to address some of the unanswered questions prior to implementation. Optimal selection for screening, possibly with the use of risk prediction models and stratification following the baseline CT, alongside robust nodule management protocols is key, as the need to ensure that screening is cost-effective and that potential harms are minimized. The feasibility of recruiting those at highest risk to screening programmes is being explored through pilot projects which will help to inform any future recommendations on implementation.

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