The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer

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Scientific summary

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Scientific summary

Background

Lung cancer: the clinical problem

Lung cancer kills more people than any other cancer. Its estimated cost to the UK NHS is £9071 per patient per year, and the total cost to the UK economy is £2.4B; more than any other cancer. The overall 5-year lung cancer survival rate in the UK is < 13%, largely due to late presentation. However, the 5-year survival with stage 1a disease is > 70%. Early diagnosis using computed tomography (CT) screening has the potential to save many lives, as well as reduce public costs.

Computed tomography screening for lung cancer

The USA-based National Lung Cancer Screening Trial recently reported a 20% relative reduction in lung cancer mortality and 6.7% all-cause mortality in subjects who were randomised to low-dose computed tomography (LDCT) scans compared with chest radiography. The final results of the Dutch–Belgian trial [NELSON: Nederlands Leuvens Longkanker Screenings Onderzoek (Dutch–Belgian Randomised Lung Cancer Screening Trial)] are due in 2017.

Successful and cost-effective screening for lung cancer is dependent upon identifying and targeting high-risk individuals, utilising algorithmic risk models that take into account known risk factors for lung cancer: tobacco use, age, previous respiratory disease, family, medical history and occupational exposures. The group selected should be of sufficiently high risk that the benefits will outweigh the likely harms.

Lung cancer screening in the UK

The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme provided funding for a pilot study of LDCT screening in the UK population to address specific questions, and inform the health service on the future implementation of lung cancer screening. The UK Lung Cancer Screening (UKLS) trial is the subject of this report. Data from the UKLS, when pooled with that from NELSON and other European trials, will potentially provide a sample of 36,000 subjects and associated mortality and cost-effectiveness figures.

Objectives

The overall aim of the UKLS pilot is to contribute to the data required for an informed decision regarding the introduction of population screening for lung cancer. This involves determining the best recruitment and screening strategies, and assessing the physical and psychological consequences and health-economic implications of screening. As the UKLS pilot is insufficiently powered to demonstrate a reduction in mortality, a further objective is to provide results for pooling with current European lung screening studies.

Main outcome measures

i. Population-based recruitment based on risk stratification.
ii. Management of trial through web-based database.
iii. Optimal characteristics of CT scan readers (radiologists vs. radiographers).
iv. Characterisation of CT-detected nodules utilising volumetric analysis.
v. Prevalence of lung cancer at baseline.
vi. Sociodemographic factors affecting participation.
vii. Psychosocial measures (cancer distress, anxiety, depression, decision satisfaction).
viii. Cost-effectiveness modelling.

Methods

The UKLS is a randomised controlled trial of LDCT compared with usual care for the early detection of lung cancer.

Primary care trust (PCT) records for 50- to 75-year-olds were used to approach individuals by letter. The Liverpool Lung Project lung cancer risk prediction algorithm version 2 was used to calculate the positive responders' risk status, who were invited. The design of the trial follows the Wald Single-Screen Design.

The UKLS pilot was undertaken in six PCTs around two specialist thoracic hospitals (Liverpool Heart and Chest Hospital, Merseyside, and Papworth Hospital, Cambridgeshire). A total of 4055 high-risk subjects were recruited and randomised in a 1 : 1 ratio to receive either a single thoracic LDCT scan or usual care. Subjects were invited to a recruitment clinic, shown a digital versatile disc, given time to discuss the trial with a research nurse, and consented. Subjects had their lung function measured, provided blood and other samples, completed detailed epidemiological, psychosocial and health economics questionnaires and were offered smoking cessation advice. The participants were randomised within a 2-week period and the CT scan group received a CT scan appointment. The CT scans were double read, using state-of-the-art volumetric analysis by radiologists and radiographers based at pilot sites. Second reads were undertaken at the Royal Brompton and Harefield NHS Foundation Trust (RBHT), London. Any nodules identified on LDCT scans were treated as defined in the UKLS care pathway protocol. Health and mortality outcomes of participants in both study arms will be followed up for 10 years, via the Office for National Statistics (ONS), the Hospital Episode Statistics (HES) database and the National Cancer Registration Service.

Classification and management of findings

The CT findings classification was based on the UKLS radiology protocol, utilising nodule diameter and volume, using the Siemens LungCARE software platform (version Somaris/5UB 10A; Siemens, Erlangen, Germany) and classified into four categories:

- no nodules or category 1 (benign) nodules – no further action required
- category 2 (small, probably benign) nodules – follow-up CT scan at 12 months
- category 3 (larger, potentially malignant) nodules – follow-up CT scan at 3 months and 12 months
- category 4 (higher chance of malignancy) nodules – immediate referral to multidisciplinary team (MDT).

When follow-up scans (3 or 12 months) were performed, the nodule volume doubling time was calculated.

Results

Demographics of trial participants

The UKLS approached 247,354 individuals in the two pilot sites, and 75,958 people (30.7%) responded positively to the screening invitation. Demographic factors associated with positive response were higher socioeconomic status, aged 56–70 years and ex-smokers. Those from lower socioeconomic groups and current smokers were less likely to respond. A total of 8729 (11.5%) positive responders were calculated as having a high risk of lung cancer. Those categorised at high risk were more often elderly, current smokers, of lower socioeconomic status and males (2.4 times more than the number of females). In total, 4061 (46.5%) of the high-risk positive responders consented to participate and 4055 were randomised.

Radiology

Computed tomography scans were read by radiologists and specially trained radiographers, who were audited, reading CT scans both independently and concurrently. Sensitivity and false-positive rates were calculated by comparing readings against reference standards; these consisted of the consensus view of radiologists at the central reading site (RBHT), including a senior radiologist with > 20 years' experience.

The mean nodule detection sensitivity for four radiographers was 71.6% (± 8.5%) compared with 83.3% (± 8.1%) for three radiologists. The number of false positives per scan ranged from 0.6 to 2.9 for the radiographers, and from 0.2 to 0.7 for the radiologists.

Our results suggest that trained radiographers are currently unsuitable to act as sole readers in lung cancer screening, but that they may improve work flow for the radiologists when developed within a lung cancer screening programme.

Results of screening

A total of 2028 high-risk trial participants were randomised to the screening arm of the UKLS, and 1994 of these received a thoracic CT scan. Overall, 979 participants had clear scans, 479 participants were scheduled for a 12-month follow-up scan, 472 participants were scheduled for a 3-month follow-up scan, and 64 participants were referred directly to the MDT. The CT scans with incidental findings that were unrelated to lung cancer were referred to the relevant MDT or their own general practitioner.

In total, 536 subjects (i.e. 472 of category 3 and 64 of category 4) had nodules requiring a repeat scan; 41 of the category 4 individuals were subsequently found to have lung cancer. However, it should be noted that a repeat CT scan at 3 months for category 3 nodules was mandated by the protocol.

Owing to our failsafe policy reflecting the single-screen design, there were a further 479 individuals for whom a repeat screen was recommended at 12 months; only one of these was found to have a confirmed cancer.

At the time of analysis, 1952 out of 1994 (97.9%) participants had completed screening in the trial, with no cancer found; and 114 individuals had been referred to the MDT, of whom 72 did not have cancer. Forty-two participants were diagnosed with confirmed lung cancer and 34 were detected at baseline or 3 months, giving a baseline prevalence of 1.7%. Thus, to date, 2.1% of all individuals screened have been diagnosed with lung cancer; 36 out of 42 (85.7%) of the screen-detected cancers were identified at stage 1 or 2. Of those with a confirmed cancer, 17 out of 42 (40.5%) were from the most deprived Index of Multiple Deprivation quintile.

We have defined false-positives in two ways, those referred to the MDT who did not have lung cancer, and those subject to repeat imaging before 12 months had elapsed who transpired not to have lung cancer (interval imaging rate). Thus on examining the number of UKLS participants referred to the MDT clinic, the false-positive rate is 3.6% (114–42/1994), whereas the interval imaging rate for the category 3 nodules is 23.2% (472–9/1994).

Psychosocial impact

The short- and long-term psychosocial impact of participation in UKLS (trial allocation and screening result) was examined with respect to lung cancer-specific distress (primary outcome) and anxiety, depression and decision satisfaction (secondary outcomes). Trial participants were asked to complete psychosocial questionnaires at baseline consent (T0), 2 weeks after either randomisation to the non-screening arm or receipt of their baseline CT scan results letter (T1), and at long-term follow-up (in January 2014, 10–27 months after attending the recruitment centre – T2).

Comparison of 2756 individuals who declined participation with 4061 individuals who attended a recruitment clinic and consented to participate indicated that women, current smokers, older individuals (aged > 70 years), those in the lowest deprivation quintile and those with a higher affective risk perception were less likely to participate. Further study attrition was observed in the same subgroups.

Analysis of the short-term impact of trial allocation indicated that, in participants with low cancer distress at baseline, those randomised to the intervention arm reported significantly higher cancer distress at T1 follow-up than controls (although not to clinically important levels). At T1, control arm participants were not very satisfied with their decision to take part compared with those in the intervention arm.

Within the intervention arm, individuals referred to the MDT as a result of a major lung abnormality reported significantly greater cancer distress and anxiety at T1 follow-up than those in any other group (clear scan, significant incidental finding or recommended for repeat scan). In the MDT referral group, the upper confidence interval (CI) for lung cancer distress approached clinically significant levels. However, those in the MDT referral group reported the highest decision satisfaction. Individuals who were recommended for a repeat scan reported significantly higher T1 lung cancer distress than those in the clear scan group and had the lowest decision satisfaction of all groups. CT scan result had no impact on depression scores at T1.

Adverse psychosocial outcomes of trial allocation and screening outcome were not evident at T2 long-term follow-up. In both T0 low- and high-scoring participants, the difference between trial arms in T2 cancer distress levels was not statistically significant. Control group participants had significantly higher T2 anxiety and depression scores than those receiving the intervention; however, the absolute differences between trial arms were minimal and not of clinical significance.

Overall, transient negative consequences were observed in individuals who were allocated to receive LDCT screening and in those who received unfavourable screening results, but these differences resolved over time and were not clinically significant. However, a profile of risk factors for trial non-uptake emerged, which must be addressed prior to routine implementation of lung cancer screening in the UK.

Health economics

Demonstrating cost-effectiveness of cancer screening requires estimation of (1) net costs of screening compared with detection via symptomatic presentation; (2) impact on (quality-adjusted) life expectancy for screened subjects; and (3) ratio of net benefits to net costs incurred [incremental cost-effectiveness ratio (ICER)].

Cost estimates were based on 2011–12 NHS tariffs. Costs incurred from the UKLS are those of screening and rescreening (£282,490), diagnostic work-up (£75,592) and treatment (£332,564), totalling £690,646 (95% CI £479,173 to £899,794). Recruitment costs and compliance were modelled from findings of other national screening programmes (e.g. UK colorectal screening). We assumed invitation and selection (risk assessment) costs of £10 per person and a participation rate of 30%. The gross current costs of the programme amounted to £754,877 (95% CI £544,824 to £966,304).

The screening benefits considered were restricted to survival gains consequent upon the screen detection of cancers. Benefits comprised life expectancy following screen detection and treatment, minus that which would have followed eventual symptomatic presentation in the absence of screening. These expectancies were modelled from existing survival data. The estimate of survival for each cancer detected was specific to gender, age and cancer stage, and we incorporated stage-dependent lead times of up to 6 years. To enable the summation of survival gains accruing at different times, we discounted future life-year gains to present values at 3.5% annually. The model predicted total life-year gains of 137.2 (discounted 89.4) from detecting and treating the 42 cancers.

The costs of managing these cancers, which would have accrued in the absence of screening at various times in the future, were offset against the gross programme costs of the UKLS. These offset costs, when discounted to present values at 3.5% annually, totalled £189,379 (95% CI £152,740 to £230,643). Net programme costs therefore amounted to £565,498 (95% CI £361,102 to £757,762).

Based on a series of assumptions used to permit exploration of cost-effectiveness in this pilot study, the ICER of screen detection compared against symptomatic detection is estimated as £6325 per life-year gained. Further exploratory analysis, using data from previous studies, to permit calculation of the cost per quality-adjusted life-year (QALY) of screening, results in an estimate of around £8500 per QALY gained for screening, subject to a number of serious uncertainties.

Conclusions

The UKLS pilot has demonstrated that it would be possible to design a cost-effective programme, with minimal adverse short-term psychosocial consequences. The 60–75 years age group is most likely to benefit from population-based screening. Rollout of screening as a service or design of a full trial would need to address issues of outreach.

Lung cancer has been detected in 2.1% of people screened. The majority of screen-detected cancers were identified at stages 1 and 2, when they are potentially amenable to curative treatment, thus resulting in greater cost savings. In any service-based screening programme, uptake would differ from that seen in a trial; nevertheless, trial data indicate some of the barriers to lung screening that would need to be considered. In order to maximise uptake, efficiency and cost-effectiveness of lung screening, it would be necessary to attempt to engage 'hard-to-reach' groups and those who perceive themselves to be at lower risk. In particular, these groups include women, older people (aged 71–75 years), current smokers, people of lower socioeconomic status and those with no prior experience of lung cancer.

Future work will consider the longer-term outcomes of the trial participants (via ONS, HES and the National Cancer Registration Service). The UKLS data will be pooled with that of the NELSON and other European Union trials in 2016, which will provide European mortality and cost-effectiveness data.

Research should also be directed towards establishing the optimum recruitment methods, frequency of screening, the best method of reading CT scans, and the longer-term psychosocial impact.

Trial registration

This trial is registered as ISRCTN78513845.

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The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

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