Lung cancer screening: what we can learn from UKLS?

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There has been almost a 1000 'lung cancer screening' papers and abstracts over the past 10 years, with half published in the last two. Avoiding the topic of lung cancer screening at respiratory, radiology and oncology conferences is becoming increasingly challenging. Is it realistic that we are going to screen for lung cancer in the UK?

We know, despite our continued efforts, that the UK health system serves its patients with lung cancer poorly. Current UK lung cancer statistics demonstrate a 13% 5-year survival attributed largely to late-stage presentation.[1] Approximately 70% of lung cancer is diagnosed at stage III and IV where options for curative treatment are greatly diminished.[2] There can be no doubt, therefore, that earlier diagnosis is crucial to improving lung cancer outcomes, and nowhere more so than the UK. However, the data supporting low radiation dose CT screening (LDCT) for lung cancer are from the USA where medicine is practised rather differently and resources not so limited. So, until this issue of *Thorax*, there has been a paucity of evidence from Britain to support the extrapolation of available data to our patients. The UK Lung Cancer Pilot Screening Trial (UKLS) reports the findings of its Wald single screen design randomised controlled pilot providing data that address many questions, but raise others.[3]

The first issue is that of determining eligibility for screening. One can reduce patient eligibility by increasing the risk threshold required to screen, thereby enriching the lung cancer detection rate and making screening cheaper. The UKLS study used the Liverpool lung project lung cancer prediction algorithm to determine eligibility. This algorithm has been shown to perform well in both internal and external validation taking into account smoking duration, family history and personal history of COPD, cancer, asbestos exposure and prior pneumonia.[4–6] As might be expected, with the demand of a 5-year lung cancer risk of 5%, this rather high threshold for screening eligibility results in a much higher baseline prevalence of lung cancer than many of the other screening studies to date (table 1). The only other screening study that had a comparable baseline lung cancer prevalence is DANTE, and this could be attributed to the high age of entry into screening, and the high current smoking rate and smoking intensity within the population studied.[7] Interestingly, as illustrated in figure 4 of the present UKLS study,[3] the investigators show that despite the required 5% 5-year lung cancer risk, most of the cancers still occurred in those over 59. This suggests that screening those aged below 59 may be of limited benefit even with a reasonably high overall risk, though the limited sample size in this pilot study means this should be interpreted with caution.

Whether a 5% threshold is appropriate to determine eligibility for a future screening programme is controversial, how many more lives would have been saved had the threshold been set lower? The higher observed lung cancer detection rate might indicate that the screening was more efficient, however this may not translate into an equivalent mortality benefit. It is likely that an older, higher risk cohort may have more comorbidities that reduce the quality and number of life years gained from detecting and treating a lung cancer early.

Another noteworthy point is the difficulty in recruiting participants to this study. Recruitment to a trial is likely to be lower than uptake of an organised screening programme due to the methods used to recruit patients. However, recruitment difficulty is a consistent theme throughout many of the CT screening studies, and this is again noted in UKLS, and most challenging in current smokers from more deprived backgrounds where most lung cancers lie.[8 9] In the present study, response rates to the initial questionnaire were low, with an initial positive response rate in the region of 40% in never smokers and former smokers but only 15% in current smokers. Furthermore, a high attrition rate was observed as potential participants were lost at every stage of the recruitment process.

As experience with CT screening is gained investigators are becoming more bullish with their definitions. The National Lung Screening Trial (NLST) investigators took false positive to mean any indeterminate nodule and hence had a very high false positive rate.[10] The investigators of the Dutch–Belgian randomised lung cancer screening trial (NELSON) greatly reduced their reported false positive rate when compared with the figure reported in NLST (23.3% in NLST vs 3.6% in NELSON) by changing the definition of false positive to include those nodules that had a baseline appearance or interval growth that supported malignancy.[11] The UKLS authors follow suit with definitions given for 'false positive' and 'interval imaging' rates thereby reducing the unpalatably high false positive rate. These definitions are probably justified. The act of being recalled for a repeat CT may generate some anxiety and distress, but studies have shown that this is rarely at clinically significant levels and is generally shortlived.[12] Having an invasive test or even a resection in the context of benign disease carries more risk of complications in addition to the increased psychological impact of such events. The 'interval imaging' rate is however, of importance, not least to evaluate costs.

Of note, the UKLS 'interval imaging' rate would likely now be lower. UKLS used a nodule management protocol based on volumetry, and nodules as small as 3 mm were reassessed by repeat CT at 1 year. After UKLS had completed recruitment, evidence from the NELSON study[11] was published and contributed to the recommendations made in the recent British Thoracic Society Guidelines for the management of pulmonary nodules.[13] In these guidelines, it is suggested that nodules <5 mm or 50 mm^3 need not undergo surveillance. Furthermore, if annual screening was taking place, it could be argued that an even larger diameter or volume threshold for active surveillance could be used in the screening nodule management algorithm and this could significantly further reduce the 'interval imaging' rate.

As acknowledged by the investigators, this is a pilot study and underpowered to detect a mortality benefit. Funding for the main UKLS study was not awarded. As a result, the cost-effectiveness analyses use data from life tables and modelled data on quality adjusted life year (QALY) gained from NLST. Although this is a significant limitation as using alternative eligibility criteria may have altered the potential mortality benefit, this is the first time actual expenditure from LDCT screening in the UK has been evaluated. The investigators have estimated an impressive cost

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Table 1 Summary of eligibility criteria and lung cancer detection rates for other screening studies[3 7 10 11 15–23]

Study	Recruitment period	Recruitment criteria	Screening methods	Cancer detection rate (%)
RCT				
NSLT	2002–2004	Age 55–74, ≥30 PY, quit<15 years ago	Annual LDCT or CXR for 3 years	1.0
MILD	2005–2011	Age>49, ≥20 PY, quit<10 years ago, no recent cancer within last 5 years	Three groups- no screen vs annual LDCT vs biennial LDCT for 5 years	0.7
ITALUNG	2004–2006	Age 55–69, ≥20 PY	Annual LDCT for 4 years vs no screen	1.4
DANTE	2001–2006	Age 60–75, ≥20 PY, quit<10 years ago, male	Annual LDCT for 4 years vs no screen	2.2
DLCST	2004–2006	Age 50–70, ≥20 PY, quit<10 years ago, FEV1>30%, able to climb two flights of stairs without pausing	Annual LDCT vs usual care for 5 years	0.8
NELSON	2003–2006	Age 50–75, ≥15 PY	Annual LDCT for 4 years vs no screen	0.9
UKLS	2011–2014	Age 50–75, ≥5% 5-year lung cancer risk as calculated by LLPv2 score	Wald single LDCT screen vs no screen	2.1
Non-RCT				
I-ELCAP	1993–2006	Age>60, ≥10 PY	Annual LDCT+CXR for 5 years	1.3
Mayo LDCT trial	1999	Age>50, ≥20 PY, quit<10 years ago	Annual LDCT for 5 years	1.4
PANCAN	2008–2011	Age 50–75, ≥2% 3-year lung cancer risk as calculated by PLCO score	Annual LDCT for 3 years	5.5 5-year rate
COSMOS	2000–2001	Age>50, ≥20 PY	Annual LDCT for 10 years	1.2
LUSI	2007–2011	Age 50–69, 'heavy' smoking history	Annual LDCT+smoking cessation for 5 years vs smoking cessation alone	1.1

COSMOS, Continuing Observation of Smoking Subjects; CXR, Chest X-ray; DLCST, Danish Lung Cancer Screening Project; DANTE, Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; I-ELCAP, International Early Lung Cancer Action Project; LDCT, low radiation dose CT screening; LLP, Liverpool lung project; LUSI, Lung Cancer Screening Intervention Study; MILD, Multi-centric Italian Lung Detection Trial; NLST, National Lung Screening Trial; PY, pack years; PANCAN, Pan-Canadian Early Detection of Lung Cancer Study; PLCO score, Prostate Lung Colorectal and Ovarian study derived scoring algorithm; RCT, Randomised controlled trial; UKLS, UK Lung Cancer Pilot Screening Trial.

of screening of only £8466 per QALY gained. This figure is vastly different to those quoted from American authors largely due to differences in local unit costs.[14] Importantly, it is well within the threshold deemed acceptable by National Institute for Health and Care Excellence and may be further reduced by refining nodule management algorithms.

The UKLS study provides invaluable data on the prevalence, stage and treatments of cancers generated by a single LDCT screening round. It also beautifully demonstrates the extent of the obstacles we potentially face with engaging the higher risk population and the need for cost-effective, yet stringent nodule management algorithms. We better get ready.

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