Screening for lung cancer: we still need to know more

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The holy grail for a screening test is that it discovers more cancers in the screened arm than in the control; that those cancers are of an earlier stage and there is, as a consequence, a stage shift towards lower stage cancers compared with the control group; that the test is acceptable to, basically, healthy individuals with low risks of serious side effects resulting from tests following a positive screen; and that the cost of a life saved, or a quality-adjusted life-year (QALY) is acceptable to the cost of a life saved, or a quality-adjusted life-year (QALY) is acceptable to the economy of the day.

Published in Thorax there is an end-of-screening report on a Danish CT-based study.1 They entered 4104 men and women, (of which 45% were women, unusually high) aged between 50 and 70 years, a 20 pack-year smoking history; lung function was recorded but was not used as an inclusion criterion. The screened group underwent five annual CTs and the control group nothing, but were seen every year. It was not stated why, or what was done to this latter group. At the end of the study period 69 cancers were found in the screened arm and 24 in the control. There were more early stage (stages I and IIB) cancers found in the screened arm than in the control arm: 48 versus 21. However, the number of advanced stage cases (IIIb and IV, and extensive disease small cell) were similar: 21 versus 16, ie, no stage shift effect.

There was also a large preponderance of adenocarcinomas and bronchoalveolar cell tumours, typical of screened populations. Also, of 611 participants followed for 5 years, 1404 non-calciﬁed nodules (NCN) were identiﬁed, another enduring problem in CT-based trials. Evaluating all deaths by the end of the study, there were 61 in the screen arm of which 15 were from lung cancer, compared with 42 deaths in total with 11 from lung cancer in the control group.

This study shows similar results to the other CT-based randomised screening trials currently in progress, with more early stage cancers found with CT compared with either nothing or a chest x-ray (CXR) in control groups. However, the overall numbers in this Danish study will be too small to show a conclusive stage shift, which could elevate screening to routine practice.

The other trials in progress, brieﬂy, include the Italian DANTE study,2 which recruited 2472 men aged between 60 and 74 years, and a 20 plus pack-year smoking history; lung function was recorded but was not used as an inclusion criterion. The screened group underwent five annual CTs and the control group nothing, but were seen every year. It was not stated why, or what was done to this latter group. At the end of the study period 69 cancers were found in the screened arm and 24 in the control. There were more early stage (stages I and IIB) cancers found in the screened arm than in the control arm: 48 versus 21. However, the number of advanced stage cases (IIIb and IV, and extensive disease small cell) were similar: 21 versus 16, ie, no stage shift effect.

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of the cost-effectiveness of NLST, based on an existing lung cancer policy model that simulates lung cancer development, disease progression, treatment and survival, was applied to each decade of the NLST population (the authors did not have access to individual data such as smoking habits). They compared estimated QALY for lung cancers based on the screening test, compared with either nothing in the control arm or the addition of a smoking cessation programme for both study arms. They also took into account smoking history, ie, 20–40 or more than 40 pack-year histories. Their study concluded that the annual screening of current and former smokers aged between 50 and 74 years costs between US$126 000 and US$169 000/QALY for a minimum of 20 pack-years of smoking, and between US$110 000 and US$166 000/QALY for a 40 pack-year minimum. If, however, the screen was linked to a smoking cessation programme that doubled the quit rate in the screened arm (and reduced the number of smoking-related deaths) the cost fell to US$75 000 for a 50 years plus and minimum 20 pack-year smoker. If screening halved the quit rate from cessation programmes, which is possible due to the ‘reassuring’ effect of a negative screen, then the cost effectiveness of screening is erased. The authors compared their data with the cost of colorectal screening versus simple control of US$13 000 to US$32 000/with the cost of colorectal screening versus simple control of US$13 000 to US$32 000. The authors compared their data with the cost of colorectal screening versus simple control of US$13 000 to US$32 000. The authors compared their data with the cost of colorectal screening versus simple control of US$13 000 to US$32 000. The authors compared their data

Another way to try to identify those who, if screened, would be more likely to have a high incidence of lung cancer would be to screen only target populations. The NLST and most other trials in progress target smokers, or ex-smokers, usually limited to 70 years of age. The UKLS trial uses the Liverpool lung project risk score to identify high-risk people, and the other current UK trial, lung SEARCH, which is based on initial sputum analysis in the screened arm is using forced expiratory volume in 1 s to include only heavy smokers with mild or moderate chronic obstructive pulmonary disease.

The lung cancer population is, in the main, elderly, of lower socioeconomic status, often with significant comorbidities, and still mainly male. It is not obviously a population that seems keen to be screened. Many individuals, by the risk taken by smoking, are risk averse and not interested in their longer-term health. There is thus the possibility of a national screening programme, should one be set up, not attracting appropriate or adequate numbers of individuals.

Silvestri et al13 showed that smokers were less willing to pay for a screening test in the USA, and less willing to undergo treatment should disease be found. They were also less willing to undergo any screening test compared with ex-smokers and never smokers.

The NLST recruited widely across the USA, and subjects were sought through the press, local mailings, advertising and the internet. Care was taken to recruit from minorities, but there is no information on the relative success of the campaign, ie, how many individuals did not wish to join. The study population was, however, representative of the high-risk smoking USA population.14 In the NELST study a questionnaire was sent to 335 441 men aged 50–75 years from population registries; 106 951 replied and subjects were chosen on their smoking habits and risk factors so as to minimise the number of recruits needed. Of these, 11 103 gave consent to the study. This represents 3.3% of all who were initially approached. There was a second round to the population in 2005, in which 250 000 questionnaires were sent and 44 509 persons replied. Of these, 4555 have been randomly selected, 1.8% of the initial population approached. In the ITALUNG trial a total of 5306 subjects was enrolled from 71 252 letters sent from 269 general practices;5 again, a low uptake of 4.5% of all subjects approached. In the DEPISCAN trial 765 subjects were recruited from 205 general practices and by 25 occupational physicians, a median of six subjects by each active centre, and only 41% of centres became active and able to find subjects. All these trials seemed to have difficulty in recruiting.

The Danish trial confirms that lead time and possibly length time bias will identify more early cancers if sought by a sensitive test, but it is too early to arrive at any conclusion about an effect on reducing mortality. This, and the other current trials, may have to be studied by a meta-analysis to see how they compare with the huge NLST, which for the present suggests that CT-based screening is worthwhile. However, cost pressures, especially with the high cost of QALY for CT screening, will drive us to a better identification of the population to screen. Even then there are challenges, both methodological, in persuading the ‘right’ people to accept a screen, in interpreting the true from false-positive results, and in driving the costs of these expensive methods down. Finally, one
Collateral ventilation and selection of techniques for bronchoscopic lung volume reduction

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Lung volume reduction can give substantial benefit to selected patients with emphysema. However, the high morbidity associated with surgery has fuelled the development of bronchoscopic lung volume reduction. Investment in research has primarily focused on the development of endobronchial valves. Three large randomised controlled trials with endobronchial valves have only shown marginal clinical benefit overall, although some patients had significant improvement in pulmonary function.1–3 Cohort studies have also demonstrated a survival benefit in patients who developed lobar atelectasis.4,5 Collateral ventilation appears to be the key factor that limits the effectiveness of endobronchial valves.6 Support for this theory has been enhanced by subgroup analysis of the Endobronchial Valve for Emphysema Palliation Trial (VENT) study, which has shown the greatest improvements in lung function (17.9% improvement in forced expiratory volume in 1 s [FEV1] at 12 months) in patients who had evidence of an intact fissure on the treatment side providing the endobronchial valves were correctly positioned.1 The absence of any clinical benefit in patients treated with incomplete bilateral lobar occlusion further supports the theory that complete isolation of the lobe is required for blocking devices to be effective.5 Spiracles or transthoracic passages were described by the late Peter Macklem as a method for reducing trapped gas in lungs when there is a high degree of collateral ventilation.7 This can be achieved in patients with emphysema by creating an artificial passage between the chest wall and emphysematous lungs with a valve that directs the flow of air out of the lung.8 However, this approach is not well tolerated by patients. An alternative strategy is to create artificial air passages within the lung and bronchial segments that allow trapped gas to escape. This technique (airway bypass) has the greatest benefit in patients with a high degree of collateral ventilation, but benefits reported so far have been only transient.9

The development of bronchoscopic treatments that are independent of collateral ventilation is essential and Ingenito et al first described the use of a fibrin glue in a sheep model of emphysema to induce lung volume reduction.10 This strategy has evolved for human use and Magnussen et al report on the use of a polymeric foam sealant in advanced emphysema.11 A polymeric solution (4.5 ml of 2%aminated polyvinyl alcohol in phosphate buffer) is mixed with a cross linker (0.5 ml of buffered pentane 1–5 dial). The mixture is then mixed with 15 ml of air to create a foam and the solution is then instilled into the target bronchial segment during flexible bronchoscopy via catheter. The air within the foam is gradually resorbed and the adherent pulmonary tissue in the treatment area also shrinks with the foam. The authors have amalgamated the data from three separate but similar clinical trial protocols and subsequently assessed treatment response according to fissure integrity based on the CT scans. The results for this study are impressive, with improvements in FEV1 of 19%, exercise capacity by 30 m and quality of life (St George’s Respiratory Questionnaire, SGRQ) by about 11 points. Furthermore, the proportion of patients who had a clinically

References