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Low dose spiral CT screening for lung cancer

Is screening for lung cancer using low dose spiral CT scanning worthwhile?

F V Gleeson

The benefits of low dose spiral CT scanning in screening for lung cancer are still under debate

Intuitively, lung cancer screening using low dose spiral chest computed tomographic (LDCCT) scanning would seem a good bet as it appears to fulfil the necessary criteria for a successful screening programme.¹ Lung cancer is very prevalent; it may be readily detected when asymptomatic using LDDCT; it may be cured at an early stage by surgical intervention; and, taking into consideration the lack of success and the possible costs of investigation and treatment in symptom detected patients, screening with LDDCT might prove to be cost effective. For LDDCT scanning to be an effective screening tool it must neither lead to an overdiagnosis bias nor to significant morbidity in patients with a false positive screen.

OVERDIAGNOSIS BIAS

The detection of clinically unimportant disease for a particular patient—or

overdiagnosis bias—has been postulated as the possible cause for the failure of one of the most analysed chest radiography screening studies performed in the 1970s, the Mayo Lung Project.^{2,3} This screening study, which used the conventional chest radiograph and randomised patients into screened and control arms, was initially reported as showing no mortality benefit between the two groups. A more recent analysis has shown that, despite a median follow up of 20.5 years, there was no significant reduction in lung cancer mortality in the screened group (337 lung cancers diagnosed, mortality rate 4.4 lung cancer deaths per 1000 patient years) compared with the control group (303 lung cancers diagnosed, 3.9 lung cancer deaths per 1000 patient years).⁴ In keeping with this potential overdiagnosis bias are published data on "clinically undiagnosed" lung cancers discovered at post mortem examination.⁵

In view of the known limitations of chest radiography for pulmonary nodule detection compared with spiral CT scanning, it would seem sensible to be concerned about an increase in overdiagnosis using the more sensitive technology.

LUNG CANCER AND NODULE DETECTION

The initial reports on the use of LDDCT scanning in screening for lung cancer have confirmed its ability to detect early stage lung cancer and its superiority in detection compared with chest radiography.^{6–10} The study most discussed is the Early Lung Cancer Action Project (ELCAP), a non-randomised prospective analysis of LDDCT scanning in which 27 lung cancers were detected in 1000 participants using LDDCT compared with seven using chest radiography.⁶ ELCAP also reported increased detection of non-calcified nodules (NCNs) using LDDCT, the majority of which were not malignant. But, perhaps the most impressive results reported by ELCAP involved the work-up of the pulmonary nodules detected, with only 28 patients having a lung biopsy, 27 of whom were confirmed to have malignancy.⁶

COMPARISON OF STUDIES

The difficulties in extrapolating data from one population and medical system to another are highlighted by MacRedmond *et al* in this issue of *Thorax*,¹¹ and two studies from the USA and two from Europe are used here for

comparison. Their results at baseline screen of 449 patients revealed a prevalence of 0.23% for non-small cell lung cancer (NSCLC) and 20.7% NCNs¹¹ compared with 2.7% and 23% from ELCAP,⁶ 1.25% and 66% from the Mayo Clinic LDDCT screening study,⁷ and 1.3% and 43% from the Munster LDDCT screening study.⁸ The 2 year incidence data from MacRedmond *et al*¹¹ found only one case of NSCLC (0.23%) and 2.5% NCNs, all visible in retrospect, compared with 0.6% and 5.3% in the ELCAP study at the first annual incidence screen,¹³ 0.65% and 23% in the Mayo Clinic study at 2 years,¹⁴ and 1.2% and 13% in the Munster study at first annual follow up.¹⁵ The study inclusion ages ranged from over 40 years (Munster) to over 60 years (ELCAP) and minimum smoking pack year histories ranged from at least 10 years (ELCAP and Dublin) to 20 years (Mayo Clinic and Munster). The prevalence and incidence data for NSCLC and NCNs from the different studies do not appear to correlate directly with either age or smoking, suggesting genuine differences in the prevalence and incidence of screen detected lung cancers and NCNs between the studies in different countries.

The impressively minimal morbidity reported by ELCAP also appears to be difficult to replicate. They report that only two of 37 biopsies performed at 2 years revealed benign disease.¹³ MacRedmond *et al* confirm one of the main concerns of radiologists relating to lung cancer screening—namely, the difficulties that would be experienced in evaluating and performing biopsy studies on the small nodules detected.¹¹ MacRedmond *et al* performed five interventions for benign disease. They performed a total of six fine needle aspiration biopsies of which four revealed benign disease, one patient subsequently went on to lobectomy, and one was complicated by a pneumothorax. In addition, one patient underwent mediastinoscopy for a benign duplication cyst. Two fine needle biopsies were false negative. Diederich *et al*¹⁵ and Swensen *et al*¹⁴ have also struggled to replicate the minimal morbidity of ELCAP, with four of 23 diagnostic procedures in Germany revealing benign disease including a thoracotomy and a video assisted thoracoscopy, and eight of 39 procedures in the Mayo Clinic study performed for diagnosis and/or cure revealing benign disease, including seven wedge excisions and one lobectomy. Using growth on follow up scanning,⁶ analysis of nodule morphology,¹⁶ nodule enhancement, and PET scanning⁹ have all been

advocated as methods of reducing interventions in patients with benign disease. Indeed, a useful spin-off from the LDDCT programmes has been the evaluation of these techniques so that they can be applied to nodules detected incidentally on non-screening chest CT scanning.

ADDITIONAL DISEASE DETECTION

Potentially, one of the benefits of lung cancer screening may be the detection of additional disease, and MacRedmond *et al* report the detection of additional incidental pathology in 49.2% of patients,¹¹ comparable to the 45.8% reported by Swensen *et al*.¹⁴ However, the definition of additional detected pathology needs clarification, with MacRedmond *et al* reporting emphysema, bronchiectasis, and CT detected coronary artery disease as significant, while Swensen *et al* only reported on additional CT findings warranting further examinations or procedures. However, even this definition enabled Swensen *et al* to detect 696 additional findings over 3 years in their study population, including breast carcinoma and atrial myxoma, from which it is assumed that the patients would have benefited. However, in 187 patients indeterminate abnormalities were detected, including 56 adrenal masses, 63 renal masses, and 28 breast nodules. It is assumed that these patients required further investigation, presumably including biopsy where necessary, for no definite benefit. This suggests that the exposure of screened patients to the potential hazards of further investigations (possibly with associated morbidity) for coincidentally detected and clinically insignificant pathology may, in fact, be a disadvantage of LDDCT.

CLINICAL EFFECTIVENESS

Swensen *et al*¹⁷ have recently reported their 5 year experience of LDDCT in a non-randomised prospective screening study of 1520 patients. Non-calcified pulmonary nodules were detected in 74% of patients, 68 lung cancers were diagnosed, and 48 participants died of various causes since the start of screening. They suggest that there was no significant stage shift or difference in the lung cancer mortality rate compared with the historical control of the Mayo Lung Project.

COST EFFECTIVENESS

In the modern healthcare environment, even if screening with LDDCT is proved to be clinically effective, the hurdle of cost effectiveness would need to be overcome to fulfil the criteria for a screening programme. This is now even of importance in the biggest spender on

health care in the world—the USA—where a recent editorial on lung cancer screening commented that “the frugal use of our health-care dollars is in the interest of the nation and in the long run the individual”.¹⁸

So, is LDDCT screening cost effective? The most fervent advocates of screening have reported on the cost effectiveness of a single baseline low dose CT scan in high risk individuals from their own ELCAP data. This showed that the incremental cost effectiveness ratio of a single baseline scan was \$2500 per year of life saved.¹⁹ Other reports both from within the USA and elsewhere are less favourable, ranging from a cost effectiveness ratio of \$51 001 per life year saved and \$88 583 per quality adjusted life year (QALY) gained,²⁰ to \$116 300 per QALY gained in current smokers and a staggering \$2 322 700 per QALY gained in former smokers.²¹

CONCLUSION

It is clear that multiple non-randomised LDDCT trials generate vast swathes of data all confirming that LDDCT can detect small pulmonary nodules, some of which are malignant; investigation of these nodules is not without risk to the patients; and that patients enrolled into these studies suffer from significant comorbidity. Unfortunately, proof of benefit is still awaited as the data from the various non-randomised studies using LDDCT currently underway appear specifically to highlight the potential pitfalls of lung cancer screening. It is also apparent that it may not be possible to extrapolate the data from studies performed in other countries and apply them to the UK. Data from the randomised controlled trials currently underway are awaited, including the results from the National Lung Screening Trial (NLST).²² This huge trial has enrolled 50 000 participants randomised to LDDCT or chest radiography and is powered to detect a reduction in mortality of 20% or greater. Nevertheless, although possibly slightly late in the day, funding for a randomised controlled trial performed in the UK may be necessary to determine unequivocally whether LDDCT would be of benefit to its citizens.

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Home oxygen services

All change for home oxygen services in England and Wales

J A Wedzicha, P M A Calverley

Changes to the home oxygen service effective from February 2006

Although it was clearly rational to increase the arterial oxygen tension of patients with chronic hypoxaemia, it was not until the publication of two key randomised controlled trials on the effects of long term oxygen therapy (LTOT) in the early 1980s^{1,2} that home oxygen services were developed in many countries where they now form an integral part of the management of chronic respiratory disability. Although these trials addressed the role of oxygen in prolonging life for patients with COPD, three main forms of home oxygen services have developed with rather different goals:

- (1) LTOT is prescribed for patients with chronic hypoxaemia ($P_{aO_2} \leq 7.3$ kPa (55 mm Hg)) for continuous use at home and is one of the few interventions to date that has been shown to reduce mortality in patients with COPD.
- (2) Ambulatory oxygen therapy refers to the provision of oxygen therapy with a portable device during exercise and daily activities.
- (3) Short burst oxygen therapy refers to the intermittent use of oxygen at

home, usually provided by stationary cylinders for periods of 10–20 minutes at a time to relieve the symptom of breathlessness. Although short burst oxygen is widely prescribed in the UK for relief of breathlessness, there is little evidence currently available for its benefit^{3,4} and delivery of cylinders to the home is costly.

In the UK, provision of LTOT through the prescription of home oxygen concentrators became available in November 1985 and since then concentrators have been installed and maintained by contractors.⁵ Although in Scotland LTOT can be prescribed in secondary care, in England and Wales oxygen concentrators can only be prescribed by primary care physicians. However, this prescription usually takes place on the recommendation of secondary care physicians and concentrators are supplied by a number of contractors on a regional basis. Thus, once patients have been assessed for LTOT in the respiratory clinic, they then have to visit their primary care physician for a prescription for the concentrator.

This process on the whole works efficiently, although there has been some difficulty in communication between primary and secondary care about the nature of the oxygen prescription.⁶ Home oxygen cylinders (usually the larger stationary 1360 litre cylinders) are also prescribed by primary care but are provided by community pharmacists and are mainly used for the provision of short burst oxygen therapy for the relief of breathlessness.

Although oxygen concentrators have been funded by the government in the UK, no formal ambulatory oxygen service has been available. Thus, if a patient requires oxygen for daily activities, this has been provided through small 230 litre cylinders and funded through hospital, charitable or private sources. Liquid oxygen for ambulatory use at home has been difficult to obtain, except on a private basis. It is interesting to speculate on why an ambulatory oxygen service was not organised at the time of the introduction of LTOT in the UK, but the reasons may include lack of good evidence for effectiveness at the time and relatively heavy early equipment for provision of liquid oxygen,⁷ together with the costs of this service. It is also possible that the lack of an organised ambulatory oxygen service has stimulated the excessive prescription of short burst oxygen therapy in the UK.

The failure to provide an ambulatory oxygen service has been an obvious gap in our provision of home oxygen and considerable discussion on this matter has taken place with the Department of Health over the subsequent years. This culminated in a report by the Royal College of Physicians on domiciliary oxygen therapy published in 1999,⁸