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Overview

What is the Optimum Screening Strategy for the Early Detection of Lung Cancer

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Abstract

Early diagnosis of lung cancer is currently the most effective way of reducing lung cancer mortality other than quitting smoking because the treatment of late stage disease has little impact. Improving the awareness of the risk of lung cancer and warning symptoms, recognition and prompt referral, and screening with low dose computed tomography (LDCT) are potential ways to improve early diagnosis. Currently the evidence is strongest for LDCT, where one large trial, the US National Lung Screening Trial (NLST), showed a 20% relative reduction in lung cancer-related mortality and a 6.7% reduction in all-cause mortality in patients who had LDCT compared with chest X-ray. Although many questions remain about optimal methodology and cost-effectiveness, lung cancer screening is now being implemented in the USA using the NLST screening criteria. Many of these questions are being answered by on-going European trials that are reporting their findings. Here we review the research evidence for LDCT screening and explore the important issues that need to be addressed to optimise effectiveness.

Key words: Computed tomography screening; implementation; lung cancer; nodules

Statement of Search Strategies Used and Sources of Information

No systematic searches were carried out for this overview. The article drew on the National Health Service evidence accredited British Thoracic Society nodule guideline and targeted searches for the latest data on computed tomography screening.

Introduction

Lung cancer is the leading cause of cancer death among men and women, with an estimated 1.8 million new diagnoses worldwide and 1.6 million deaths each year (2012) [1]. In developed countries, a reduction in tobacco smoking has caused a dramatic reduction in age-standardised incidence rates. However, crude incidence continues to increase, an effect explained by the ageing population. Lung cancer survival is much lower than other common cancers and for the period 2005–2009, 5 year survival was only 9.0% in the UK and 15% in Sweden and Canada [2,3]. The main reasons why lung cancer outcomes are so poor are that around 70% of patients first present to specialist care with advanced disease and current treatment at this stage has very little effect on mortality. This applies across all age groups and in all countries. Curative treatments for lung cancer through surgery or radical radiotherapy are only available for the few people with cancers diagnosed in the early stages. To improve lung cancer mortality, earlier diagnosis is essential and the most promising approach is screening with low dose computed tomography (LDCT). In LDCT screening trials, the stage distribution is reversed, with over 70% of lung cancers detected at an early stage (I or II), with subsequent high rates of surgical resection [4–6].

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The Evidence for Low Dose Computed Tomography Screening

The National Lung Screening Trial

The National Lung Screening Trial (NLST) randomised 53 454 people aged 55–75 years with at least a 30 pack-year smoking history, who were current smokers or had quit within 15 years, to either three annual LDCTs or three annual chest X-rays [7]. This trial was halted 1 year earlier than planned as the pre-specified relative reduction in lung cancer mortality of 20% had been achieved in the LDCT arm. Unlike many randomised trials of screening in other tumours, there was also a significant reduction in all-cause mortality of 6.7% in the LDCT arm. Although NLST was the first trial to show a reduction in lung cancer mortality, it has been argued that more trials are needed to confirm the findings. However, when the findings of NLST are examined in more detail, the results become more convincing rather than less: the reduction in lung cancer mortality was achieved despite many patients being at relatively low risk of lung cancer. The NLST authors have since shown that the number needed to screen to prevent one death was 5276 in the lowest quintile of risk, falling to 171 and 161 for the two highest quintiles [8]. It has also been shown that by applying a risk prediction model ($PLCO_{m2012}$) set at a risk threshold of 1.51% risk of cancer over 6 years rather than the entry criteria set by the US Preventive Services Taskforce (based on NLST), that 8.8% less people would be screened but with 12.4% more cancers detected [9]. The number needed to screen is important because it is the reciprocal of the absolute risk reduction. Overall, in NLST the number needed to screen was 320 (absolute risk reduction in lung cancer mortality of 0.31%).

Other Randomised Controlled Trials of Low Dose Computed Tomography Screening

The NEderlands-Leuvens Longkanker Screenings ONderzoek (NELSON) trial, is the largest European trial having randomised 15 422 subjects; it is powered at 80% to show a lung cancer mortality reduction of at least 25%, 10 years after randomisation [10–12]. The results are eagerly awaited. Eligible participants were those aged 50–75 years who were current or former smokers (within 10 years) of either >15 per day for >25 years or >10 per day for >30 years. Semi-automated volumetry was used to evaluate smaller lung nodules that were classified as indeterminate if 50–500 mm^3 or positive if >500 mm^3. Participants with an initial indeterminate result underwent an interval LDCT and volume doubling time (VDT) was used to define a growth rate worthy of further work-up (<400 days).

The UK Lung Screening (UKLS) trial randomised over 4000 patients in its pilot phase and used similar pre-specified algorithms for the management of indeterminate nodules as NELSON [13]. The UKLS used a single screen, so a lower limit of nodule volume and diameter prompting further imaging (15 mm^3) was specified than for NELSON. UKLS also differed from many of the other studies, in that recruitment was via a randomised population postal approach to people within the eligible age group followed by an individual risk stratification questionnaire for lung cancer with a validated risk assessment tool. NELSON recruited subjects through random samples from age bands of the population followed by selection on the basis of smoking habit. The eligible population in NELSON was 19% of those who responded to the initial invitation questionnaire compared with 11.5% in UKLS, probably reflecting a higher risk threshold in UKLS [14].

Other European trials that have compared LDCT with either plain chest radiograph or usual care include the Multi-centric Italian Lung Detection Trial (MILD) [15], the Detection And screening of early lung cancer by Novel imaging TEchnology and molecular assays (DANTE) [16,17], the Danish Lung Cancer Screening Trial (DLCST) [18], the German LUng cancer Screening Intervention (LUSI) [19], the Italian Lung cancer Computed Tomography screening Trial (ITALUNG) [20] and Depiscan [21], a French pilot study.

The DLST, DANTE and MILD studies have reported mortality figures that show no significant reduction in lung cancer mortality; the relative risk of lung cancer mortality was found to be 1.03 (0.66–1.6), 0.99 (0.69–1.43) and 1.50 (0.62–3.60), respectively. However, these trials were all underpowered with a combined total subjects randomised of 10 675, one-fifth of NLST. When these results are added to NLST, they make little difference to the overall mortality reduction [22].

In response to NLST, the US Preventative Services Taskforce (USPSTF) commissioned an independent review of the evidence for LDCT and recommended that LDCT screening should be offered annually for people aged 55–80 years with the same entry criteria as for NLST [23]. Since then, healthcare insurers Medicare and Medicaid have agreed to fund LDCT screening for those aged 55–77 years old with a >30 pack year history of current smoking or former smokers who have stopped within 15 years [24]. Most recent international consensus statements on LDCT screening have accepted that efficacy in reducing lung cancer mortality has been shown, but have noted that more work needs to be done to ensure screening programmes are clinically and cost-effective.

Optimising Low Dose Computed Tomography Screening

Most of the factors that should be optimised for programmes to be most effective have been identified in international consensus statements [25]:

- The optimal risk populations that would benefit from screening.
- The radiological protocol for computed tomography screened nodules to reduce the need for invasive investigations.
- The screen interval and number of screening rounds.
- The optimal work-up and treatment of positive findings.
- The cost-effectiveness of LDCT screening.

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